Position Statement of the Immunonephrology Working Group of the Portuguese Society of Nephrology on the Use of Belimumab in Lupus Nephritis

Estela Nogueira[1,2*], *Nuno Oliveira*[3,4*], *Iolanda Godinho*[1,2], *Alice Lança*[1,2,4], *António Inácio*[5], *Clara Santos*[6], *Helena Pinto*[3,4], *Ivo Laranjinha*[7], *Raquel Vaz*[8], *Sofia Oliveira Correia*[9,10,11], *Teresa Jerónimo*[12], *Inês Ferreira*[13]

On behalf of the Immunonephrology Working Group of the Portuguese Society of Nephrology

*equal contribution

1. Serviço de Nefrologia e Transplantação Renal, Unidade Local de Saúde Santa Maria, Lisboa, Portugal
2. Centro Académico de Medicina de Lisboa, Lisboa, Portugal
3. Serviço de Nefrologia, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
4. Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal
5. Serviço de Nefrologia, Unidade Local de Saúde Arrábida, Setúbal, Portugal
6. Serviço de Nefrologia, Unidade Local de Saúde Gaia Espinho, Gaia, Portugal
7. Serviço de Nefrologia, Unidade Local de Saúde Lisboa Ocidental, Lisboa, Portugal
8. Serviço de Nefrologia, Unidade Local de Saúde de Braga, Braga, Portugal
9. Serviço de Nefrologia, Unidade Local de Saúde Santo António, Porto, Portugal
10. Unidade Multidisciplinar de Investigação Biomédica, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal
11. Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal
12. Serviço de Nefrologia, Unidade Local de Saúde do Algarve, Faro, Portugal
13. Serviço de Nefrologia, Unidade Local de Saúde São João, Porto, Portugal

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Abstract

Systemic lupus erythematosus (SLE) is a challenging immune-mediated disease that frequently involves the kidney as lupus nephritis (LN), an immune complex glomerulonephritis. Its occurrence is associated with increased morbidity and mortality and current treatment still fails to preserve renal function in the long term. As such, more efficacious and less toxic treatments are needed to treat LN, aiming to reduce renal relapses and improve renal survival. Belimumab, an inhibitor of the soluble B-cell activating factor became the first biologic agent approved for the treatment of SLE and is now approved as an add-on therapy for LN. Herein, the Immunonephrology Working Group of the Portuguese Society of Nephrology reviewed the scientific evidence that led to belimumab´s approval in recent LN guidelines and exposed its perspective on the use of belimumab in LN in Portugal.

Keywords: Antibodies, Monoclonal, Humanized/therapeutic use; Belimumab; Lupus Nephritis/drug therapy

INTRODUCTION

Systemic lupus erythematosus (SLE) is a challenging immune-mediated disorder that can involve multiple organs during its relapsing-remitting course. Kidney disease can occur at presentation or during relapses in 30% to 70% of patients, depending on their geographic origin and ethnicity.[1,2] Although survival of SLE patients with lupus nephritis (LN) has significantly improved over the last decades, LN is still associated with progression to end-stage kidney disease (ESKD) in 25% to 30% of patients at 15 years.[3-5]

Despite advances in LN treatment, the complete renal remission rate is still significantly low, raising the need for more efficacious drugs.[3] In a recent nationwide

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* **Corresponding Author:** Estela Nogueira | estelanogueira@gmail.com | Av. Professor Egas Moniz 1649-035 Lisboa.

multicenter Portuguese cohort of 260 LN patients, only 62% reached complete renal remission at one year. [4]

Moreover, current treatment still relies on significant doses of glucocorticoids (GC), which substantially reduce patients' health-related quality of life and are associated with severe long-term toxicity-related consequences. As such, it is of paramount importance to develop therapeutic regimens with increased efficacy, that improve remission rates and allow flare reduction with kidney function preservation along with glucocorticoid sparing. Recently, lupus nephritis KDIGO 2024 and EULAR 2023 guidelines were published and included new drugs as part of combination therapeutic regimens, namely belimumab and voclosporin.[5,6]

This position statement will review the evidence behind belimumab's approval by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) and disclose the Immunonephrology Working Group (IWG) of the Portuguese Society of Nephrology (SPN) perspective on belimumab use in lupus nephritis in Portugal.

B-CELL TARGETING IN LUPUS NEPHRITIS

SLE pathogenesis is associated with loss of self-tolerance and development of autoreactive B cells that secrete autoantibodies toward endogenous nuclear and cytoplasmic material.[7] Therefore, B-cells have been a therapeutic target for decades, either focusing on drugs that promote their depletion (anti-CD20 rituximab and obinutuzumab) or reduce their survival, proliferation and differentiation (namely belimumab).

BELIMUMAB

Belimumab is a recombinant human immunoglobulin G1λ monoclonal antibody that binds to soluble B-cell activating factor (BAFF). BAFF is a member of the tumor necrosis factor (TNF) ligand superfamily of proteins and is generally produced by myeloid and stromal cells.[8] B-cell survival, differentiation and antibody production is associated with BAFF stimulation of three B-cell receptors: BAFF-Receptor, transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA). Studies have reported increased BAFF levels in SLE patients and a correlation with disease activity.[8]

Therefore, several drugs have been developed to inhibit BAFF pathway, namely belimumab. It can be administered intravenously (10 mg/kg q2 weeks x3 doses, then 10 mg/kg q4 weeks; 1 hour perfusion) or subcutaneously (400 mg q week x 4 doses, then 200 mg q week), and dose adjustment is not needed in patients with renal impairment. It is generally well tolerated and most studies do not report an increase in adverse events when associated with standard of care (SoC) therapy. Although suicidal ideation has been reported, this secondary effect has not been confirmed in other studies. However, its use should be made with caution in patients with depression. Hypersensitivity reactions can occur; as such, an antihistamine (with or without analgesic) can be given in the first 2 administrations; these should occur under clinical supervision, with a few hours of post-administration vigilance. The most frequently reported adverse events are bacterial (respiratory and urinary) and viral infections, diarrhea, nausea and leukopenia.[9]

Belimumab is not approved for pregnant or lactating patients, and although its use has been increasingly reported, data on its safety remains sparse and should be avoided. No antibacterial prophylaxis is recommended.[9]

ROLE OF BELIMUMAB IN THE TREATMENT OF SLE

In 2011, belimumab became the first biologic agent approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of SLE.

Evidence that supports its efficacy in SLE comes from two phase III trials, BLISS 52 and BLISS 76.[10,11] Both studies showed that belimumab improved Systemic Lupus Erythematosus Responder Index (SRI-4) at week 52 compared to SoC (GC alone or combined with another immunosuppressive agent), reduced SLE clinical and serological activity (decreased dsDNA levels and improved complement consumption), lowered severe flare rate, allowed for GC sparing and was generally well tolerated.[10,11]

Additionally, four more phase III trials were conducted: three met their primary endpoint, proving belimumab's efficacy in a North East Asian SLE population and of its subcutaneous form of administration; the fourth trial, EMBRACE, did not achieve its primary endpoint in SLE patients of black race, but belimumab still improved SLE disease activity.[12-15]

Real-world data have also demonstrated belimumab's efficacy in improving disease activity, treating musculoskeletal, mucocutaneous and renal manifestations, reducing *de novo* renal disease, severe and non-severe flares, as well as decreasing damage accrual and allowing for GC sparing.[16,17]

ROLE OF BELIMUMAB IN THE TREATMENT OF LUPUS NEPHRITIS

Although previous belimumab trials have excluded patients with severe active LN, many patients had previous LN or low-grade proteinuria. Several trials, as well as real-word data have demonstrated that belimumab can reduce de novo or LN flares and proteinuria.[9-17]

This evidence led to the development of phase III Belimumab International Study in Lupus Nephritis trial (BLISS-LN), which would specifically evaluate belimumab efficacy as add-on to SoC (mycophenolate mofetil-MMF or cyclophosphamide–azathioprine; CYC-AZA) in patients with LN class III to V, with proteinuria >1 g/day.[18] In the BLISS-LN trial, the primary endpoint was set at week 104

and named primary efficacy renal response (PERR, meaning urinary protein-to-creatinine ratio ≤0.7 g/g, estimated glomerular filtration rate [eGFR] no worse than 20% below the preflare value or ≥60 mL per minute per 1.73 m^2 of body-surface area, and no use of rescue therapy).

Many trials have failed to achieve their primary endpoint due to stringent proteinuria goals or too short time to evaluate efficacy, namely complete renal response (CRR) at 6 months; these considerations could explain why rituximab despite having failed to achieve its primary endpoint in EXPLORER and LUNAR trials, is still used off-label in SLE and is considered a possible approach for refractory LN according to guidelines. Further analysis of LN trials has revealed that proteinuria <0.8 g/day at 12 months after randomization was the single best predictor of good long-term renal function (sensitivity 81% and specificity 78%). The addition of serum creatinine (sCr) to proteinuria as a composite predictor did not improve the performance of the outcome measure, nor did the addition of urinary red blood cells (RBCs).[19]

This data led to the definition of PERR in the BLISS-LN. The trial included 448 patients (224 in each group) and PERR was achieved in significantly more patients (43% *vs* 32% odds ratio 1,6; *p*=0.03) at week 104. The major secondary endpoint, CRR (defined as any of the following: urinary protein-to-creatinine ratio <0.5, eGFR no worse than 10% below the preflare value or ≥90 mL per minute per 1.73 m^2, and no use of rescue therapy) was also reached in 10% more patients at week 104 in the belimumab group (30% *vs* 20%; odds ratio 1,7; *p*=0.02). The risk of a renal-related event (defined as any of the following: ESKD; doubling of sCr; renal worsening as evidenced by increased proteinuria and/or impaired renal function; renal disease-related treatment failure) or death was lower among patients who received belimumab compared to placebo (HR, 0.51; *p*=0.001). The safety profile of belimumab was similar in both groups.

Further analysis showed that PERR results on the belimumab group were essentially driven by proteinuria (OR 1.5; 1.0-2.3) and absence of treatment failure without the need for rescue therapies, particularly with steroids (OR 1.65; 1.0-2.6); no statistical significance was achieved on eGFR parameters (OR 1.3; 0.9-1.9). Subgroup analysis also showed that the PERR results on the belimumab group were mostly driven by the MMF subgroup (OR 1.6; 1.0-2.5); in the CYC-AZA subgroup, the percentages of patients with a response were equivalent in the belimumab and placebo groups (OR 1.5; 0.7-3.5). The overall percentage of black patients was small (around 13%), but these patients appeared to have a more frequent PERR and CRR when in the belimumab group, although with a lower overall proportion when compared with the entire study population.[18] This limited data should be taken into account when considering prescription of belimumab in this population.

Post-hoc analysis of BLISS-LN trial revealed that benefits of belimumab in kidney outcomes (PERR and CRR) were consistent in newly diagnosed and relapsing patients, with or without GC pulses at induction and that response was driven by the proliferative component of LN (not pure class V), especially in patients with urinary protein/creatinine ratio under 3 g/g.[20-21]

Although there is more evidence in proliferative LN with low-grade proteinuria, belimumab significantly reduced the risk of kidney-related events or death and lupus nephritis flare in the overall population, independently of LN class or proteinuria level. It also lowered the risk of a sustained 30% or 40% decline in eGFR and attenuated the annual rate of eGFR decline (annual eGFR slope, placebo *versus* belimumab; -5.72 *vs* 2.12 mL/min/year, *p*=0.0407).[21] Furthermore, an open-label extension of 28 weeks of BLISS-LN concluded that belimumab was well tolerated and kidney outcomes remained consistent during that time.[22]

REAL-WORLD EVIDENCE OF BELIMUMAB USE IN LUPUS NEPHRITIS

The beneficial effects of belimumab were also replicated in real-life populations. Concerning non-renal SLE, real-world evidence regarding belimumab use is consistent with results from main clinical trials, showing reductions in SLEDAI score, prednisone-equivalent dosing, and flare frequency (12 months prior to belimumab to 12 months after belimumab: 1.15 *vs* 0.39 mean flares per patient per year; 66% reduction); Long-term data (up to 2 years post-treatment initiation) is also consistent with continuous improvement of SLEDAI score and GC sparing among patients remaining on therapy.[23]

Data regarding LN outcomes remains limited. In a nationwide, multicentric cohort, that included 91 patients with cSLEDAI>0 despite SoC, positive dsDNA and/or low complement and renal activity (defined as the fulfillment of SLEDAI-2K renal items and/or eGFR<60 mL/min/1.73m^2), that were treated with belimumab, 64 (70.3%) achieved PERR during follow-up, after a median time of 6 months (6-12), of whom 38% reached CRR.[23] Among the patients who achieved PERR at 6 months and completed follow-up, 86.7% maintained the response at 24 months. This trial confirmed the glucocorticoid-sparing effect of belimumab and a significant improvement in serological activity.[23] In contrast to BLISS-LN, in this study, mean proteinuria was 0.8 g/d (0.5-1.6) and belimumab was started after initial treatment due to persistent activity; 23% of the patients were not under immunosuppression beyond glucocorticoids or antimalarials at the time of belimumab initiation.[23] This data might support the utility of a precocious use of belimumab in patients with persistent low to moderate proteinuria, in order to maximize the possibility of achieving a timely and complete renal response.

Another observational real-life trial from a Chinese population with 61 LN patients showed similar results, with belimumab improving renal response and SLEDAI scores while reducing GC exposure.[24]

Additionally, a study with protocoled kidney biopsies also demonstrated that belimumab added to SoC could increase the possibility of achieving a complete histological response.[25]

In all these trials, belimumab was generally well tolerated, with a good safety profile and no new adverse effects concerning the drug were identified.[23-26]

BELIMUMAB POSITIONING IN CURRENT INTERNATIONAL TREATMENT GUIDELINES

Following the publication of BLISS-LN and its post-hoc analysis, belimumab was approved by the FDA (2020) and EMA (2021), for the treatment of adult SLE patients with active LN.

International guidelines later updated their recommendation, incorporating belimumab in the treatment of LN. As such, 2023 EULAR recommendations for the management of SLE considered that combination therapy with belimumab plus either CYC or MMF can be considered upfront for the treatment of patients with active proliferative LN (evidence 1b/A).[6]

Similarly, KDIGO 2024 recommendations for the management of LN also suggest the use of a triple immunosuppressive regimen of belimumab with GCs and either MMF or reduced-dose CYC in patients with class III/IV+V. Additionally, the KDIGO Working Group considers that this regimen should be preferred in patients with repeated kidney flares or at high-risk for progression to kidney failure due to severe chronic kidney disease (CKD).[5]

BELIMUMAB USE IN PORTUGAL

In Portugal, belimumab is available for the treatment of SLE patients since 2014, as an additional therapy for active disease despite optimized SoC therapy (or intolerance to SoC), defined by SELENA-SLEDAI >10, active immunological activity (dsDNA titers >30 UL/mL and low complement), and without renal or central nervous system involvement.[9]

Despite being approved to treat LN class III/IV (+V) by FDA and EMA and being endorsed by most recent EULAR and KDIGO guidelines, Portuguese regulatory authorities (Autoridade Nacional do Medicamento e dos Produtos de Saúde - Infarmed) considered that belimumab did not report an added value regarding renal remission, renal function deterioration and progression to CKD and renal relapse in the treatment of LN compared to SoC.[27]

The evaluation raised concerns that the reported benefits of belimumab in LN treatment were essentially based on its antiproteinuric effect, and that this outcome, although generally used as a surrogate marker for kidney disease progression, was not validated in the SLE population. Additionally, the regulatory authorities considered that the submitted data was unable to prove a beneficial effect in preventing the deterioration of kidney function and progression to ESKD, as baseline GFR was unavailable in 46% of patients, meaning that PERR and CRR were driven mainly by proteinuria reduction. Moreover, the composite outcome PERR was considered of uncertain clinical value as it was used for the first time in LN trials.

Although all these concerns are relevant, the final conclusion derived from them - lack of benefit - is extremely debatable.

As was already discussed, BLISS-LN was a positive trial, with more patients in the belimumab group reaching PERR and CRR outcomes than in the placebo group (PERR 43% *vs* 32%; OR 1.6; CI 1.0-2.4; P= 0.03; CRR 30.0% *vs* 19.7%; CI 1.11-2.74;OR 1,74; *p*=0.016). However, these results were mostly driven by proteinuria (PERR- OR 1.5; 1.0-2.3; CRR -OR 1.58; CI 1.05 - 2.38; *p*=0.0268) and absence of treatment failure without the need for rescue therapies, particularly with steroids (OR 1.65; 1.0-2.6); no statistical significance was achieved on eGFR parameters (OR 1.3; 0.9-1.9).[18]

It is important to underline that proteinuria reduction is indeed a surrogate outcome of the primary goal in treating LN (or any other kidney disease)- that is preserving kidney function and avoiding the need of renal replacement therapies. Additionally, this outcome is strongly supported by evidence, deriving not only from clinical nephrology literature in general, but also from LN literature.[28-33]

Concerning non-LN literature, a meta-analysis by the CKD Prognosis Consortium demonstrated association of ACR >30 mg/g or +1 protein in urine strip test with risk of all-cause and cardiovascular mortality, kidney failure, AKI and CKD progression, both in the general population and in populations with increased risk for cardiovascular disease.[28] Based on this data, the KDIGO guidelines on CKD, consider that an albuminuria >30 mg/g or >300 mg/g places a patient at a moderately increased risk and high risk, respectively, of CKD progression.[29]

More recently, and concerning IgA nephropathy (IgAN), an immune-mediated glomerulonephritis, the Kidney Health Initiative project performed a critical review of the data on proteinuria reduction as a surrogate endpoint for a treatment's effect on progression to ESKD.[29] The workgroup epidemiologic data indicated a strong and consistent relationship between the level and duration of proteinuria and loss of kidney function; analyses of data from 13 controlled trials also revealed an association between treatment effects on percent reduction of proteinuria and a composite of time to doubling of serum creatinine, ESKD, or death. This data allowed for the conclusion that, in IgAN, proteinuria reduction was reasonably likely a surrogate endpoint for a treatment's effect on progression to ESKD.[29]

Regarding LN, proteinuria is also one of the primary renal outcomes evaluated in clinical trials. In the Aspreva Lupus Management Study (ALMS), a landmark trial that helped establish the routinely use of MMF for the treatment of proliferative LN, the primary outcome was renal response

at week 24, defined by the degree of proteinuria reduction and stabilization or improvement of serum creatinine.[30] Further analysis of ALMS data identified a reduction of proteinuria by >25% by week 8 as being predictive of renal response at week 24 (OR 3.2; $p<0.05$).[31]

Even more relevant for the present discussion, analysis of long-term follow-up data from the Euro-Lupus Nephritis Trial, another landmark trial in LN that helped establish the role of low-dose CYC and sequential therapies in LN, emphasized the importance of proteinuria reduction as a marker for achieving a good long-term renal outcome. In a multivariate analysis, after a median follow-up of 73 months, the positive predictive value of a 75% decrease in proteinuria at 6 months for good long-term renal outcome was 90%; the positive predictive value of a 24-hour urinary protein level <1 g at 6 months for good long-term renal outcome was 87% (OR 6.3; CI 1.2-34.4; P=0.03).[32]

Further analysis of long-term follow-up data from the same trial, including 76 patients with minimum follow-up of 7 years, evaluated the performance of proteinuria, sCr, and urinary RBCs as predictors of good long-term renal outcome. Definition of good long-term renal outcome was defined as sCr ≤1.0 mg/dL at least 7 years after entry into the trial; conversely, patients with sCr >1.0 mg/dL and those who developed ESKD at any time were considered as having a poor renal outcome. A proteinuria value of <0.8 g/day at 12 months after randomization was the single best predictor of good long-term renal function (sensitivity 81% and specificity 78%). The addition of sCr to proteinuria as a composite predictor did not improve the performance of the outcome measure; the addition of urinary RBCs as a predictor significantly decreased the sensitivity to 47%. This study demonstrated that the level of proteinuria at 12 months was the individual best predictor of long-term renal outcome in patients with LN.[12] This data conclusively demonstrates the importance of proteinuria reduction as an outcome for evaluating the efficacy of the treatment in LN.

All these facts are acknowledged by the FDA, which considers a response in proteinuria (protein-creatinine ratio) as one of the components of CRR (the other being preservation/improvement of renal function by eGFR), that can be used as surrogate endpoint in LN trials, as a basis for drug approval or licensure.[33]

As previously mentioned, the favorable response to belimumab derives mostly from proteinuria reduction and the data that is presented in this document validates the relevance of proteinuria in predicting the long-term renal outcome in the LN population; thus, we cannot agree with the Infarmed statement dismissing the importance of proteinuria reduction because it is not well validated in the LN population. Proteinuria reduction is a critical goal in LN treatment, predicting CKD progression in this population. Consequently, we support that any drug that consistently demonstrates a significant and sustained impact in this parameter should be considered for the treatment of LN.

Another major concern raised by Infarmed was that BLISS--LN was unable to conclusively demonstrate a favorable impact of belimumab in preventing kidney function deterioration and progression to ESKD, and that in a significant number of patients (46.6%) the preflare eGFR was unknown.

Evaluating the impact of a drug on kidney function is an exceedingly difficult proposition, since many kidney diseases have a smoldering course over many years, making it difficult to capture any eventual benefit during the usually limited time frame of a clinical trial; hence the need of surrogate markers such as proteinuria, that we have just discussed. This is an obvious and very pertinent concern, that can only be solved through commitment to long-term clinical follow-up of LN clinical trial cohorts, through many years/decades; it is fully recognized by the 2024 KDIGO Guidelines, stating that, with regard to kidney function preservation, the only long-terms robust data available is the one proving the superiority of steroids plus cyclophosphamide versus steroids alone and long-term data is relatively scarce for all other regimens.[5]

We already stated that the eGFR component of the PERR did not achieve statistical significance in BLISS-LN, despite the absolute number of patients achieving an eGFR <20% below preflare value or above 60 mL/min being higher in the belimumab group. The percentage of missing data from preflare eGFR may have impaired the achievement of statistical significance on this item; also, it should be noted that 59% of the patients had a baseline eGFR >90 mL/min and this could also compromise the demonstration of a favorable impact of belimumab on this item since most of the patients in the trial had a preserved kidney function at baseline.

Nevertheless, this does not exclude that belimumab may have a favorable impact in preserving kidney function.

Indeed, a secondary analysis from BLISS-LN showed that the annual rate of decline in eGFR appeared to be less in the belimumab group than in the placebo group between weeks 24 and 104, in both the on-treatment and on-study analysis (although only reaching statistical significance in the on-study group). In this same analysis, in both the on-treatment and the on-study groups, belimumab significantly reduced the risk of having a 30% and 40% decline in eGFR between baseline and week 104 when compared to placebo. Moreover, a sustained 30 and 40% decline in eGFR from baseline until the end of the study was significantly less reported in the belimumab group.[20-22] The 30% and 40% eGFR thresholds are important, since they are generally considered to be predictors of progression to ESKD.[34] Altogether, this data shows that belimumab has a favorable impact in preserving kidney function- the major goal of treatment in LN, and is considered significant by the KDIGO 2024 Guidelines Working Group.[5] The 2-year duration of the BLISS-LN trial also provided an opportunity to assess the effectiveness of belimumab in preventing

renal flares. Secondary analyses from BLISS-LN showed that belimumab reduced the risk of LN flare by 55% during the last 18 months of the trial (HR 0.45; CI 0.45-0.72; *p*=0.0008).[20-22] Reducing LN flares is also fundamental as it prevents the accumulation of chronic kidney damage, which is critical for achieving a favorable renal outcome.

So, despite the inevitable limitations of clinical trials and the dependence on surrogate-markers such as proteinuria, we feel confident that the evidence we just presented is robust enough to recommend the use of belimumab for the treatment of LN, if not in all patients, at least in selected patients (as will be discussed in the next section). Considering that major international guidelines were updated to include belimumab, we strongly believe that Portuguese patients should have the same opportunities than other European patients to access this therapy. As such, the IWG of the SPN urges Infarmed to consider our views on the subject and to take into account which patients would probably benefit the most from belimumab combination regimens.

CONSENSUS RECOMMENDATION ON THE USE OF BELIMUMAB IN LUPUS NEPHRITIS BY THE IMMUNONEPHROLOGY WORKING GROUP OF THE PORTUGUESE SOCIETY OF NEPHROLOGY

Recent EULAR and KDIGO LN guidelines have incorporated belimumab as a possible option in the treatment of LN, focusing the discussion on whether belimumab should be initiated early, as part of a combination therapy with the SoC—which includes MMF or low-dose CYC, alongside GC—or whether it should be reserved for relapsing or refractory disease.

It is worth reviewing the arguments clearly stated in the 2023 EULAR recommendations. The upfront use of belimumab relies on the facts that: LN is a severe disease with increased morbidity and mortality, which leads to progressive and cumulative nephron loss and CKD; rates of complete response at 1–2 years with SoC therapy (ie, control arms) in recent clinical trials (including BLISS-LN) are consistently low (in the range of 20%–30%); finally, based on its RCT, belimumab was approved for all patients with active LN, meaning that all patients can potentially benefit from this drug, including as first-line treatment.

On the other hand, systematic belimumab use substantially increases treatment costs and has the potential for unnecessary treatment in patients that would respond to MMF or low-dose intravenous CYC alone - this argument is particularly relevant, since real life data reports higher response rates with SoC when compared to reported rates from RCT.[35,36]

As such, it is the position of the Immunonephrology Working Group of the Portuguese Society of Nephrology that the use of belimumab for the treatment of active LN should be weighted and we recommend that it should be particularly considered in the following subgroups of patients:

1. LN histological classes III or IV +/- V, with baseline urine protein-creatinine ratio (UPCR) <3 g/g;
2. Previous kidney flares;
3. Inadequate response to SoC (based on expected proteinuria reduction >25%) by 3–6 months of treatment induction (following confirmation of therapeutic adherence, and adequate dosing of immunosuppressive medications), especially if immunological activity persists;
4. High-risk for medium/long-term progression to kidney failure due to chronic kidney disease (histological chronicity, persistent proteinuria and persistent immunological activity);
5. Increased risk of glucocorticoid-related adverse events that imply the need of steroid-sparing strategies (e.g. high previous cumulative dose of steroids or steroid toxicity, diabetes, obesity, osteoporosis, psychiatric disorders, …);
6. Active LN and extra-renal manifestations (skin, joints, serositis…) with intense serological activity (preferably in those that respond poorly to SoC).

In patients with irregular therapeutic adherence, the administration of belimumab should preferably be intravenous. Finally, it should be stressed that LN patients treated with belimumab in BLISS-LN had relatively preserved kidney function (59% had eGFR >=90 mL/min) and that patients with eGFR <30 mL/min, dialysis dependency and those with previous treatment failures with MMF and CYC were excluded from the trial. Thus, in patients with rapidly progressive kidney failure or refractory disease, other options should be considered alternatively to belimumab (after properly excluding non-compliance, inadequate dosing and eventually repeated kidney biopsy).

Patients treated with triple immunosuppressive regimens (belimumab in addition to SoC) should continue with a triple immunosuppressive regimen as maintenance therapy for 2.5 years.

Ethical Disclosures

Conflicts of Interest: Estela Nogueira – Occasional consulting and lecturing fees (GSK, Vifor pharma and Otsuka); Nuno Afonso – Occasional consulting and lecturing fees (GSK, Viforpharma and Alexion); Inês Ferreira – Occasional consulting (GSK and Vifor pharma); Iolanda Godinho –Nothing to disclose; Alice Lança – Nothing to disclose; António Inácio – Nothing to disclose; Clara Santos – Nothing to disclose; Helena Pinto – Nothing to disclose; Ivo Laranjinha – Occasional consulting and lecturing fees (Viforpharma and Novartis); Raquel Vaz – Nothing to disclose; Sofia Correia – Nothing to disclose; Teresa Jerónimo – Occasional consulting and lecturing fees (CSL Vifor).

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