Clinical Efficacy of Routinely Administered Belimumab on Proteinuria and Neuropsychiatric Lupus

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Background and Objectives: Belimumab (BEL) is a monoclonal antibody approved for the treatment of active systemic lupus erythematosus (SLE) but not for lupus nephritis (LN) and neuropsychiatric systemic lupus erythematosus (NPSLE). We aimed to assess BEL’s effects on these severe, potentially life-threatening manifestations.

Methods: Retrospective observational cohort study using routine clinical data in a case series of patients with SLE receiving BEL.

Results: Sixteen patients received BEL therapy for active SLE. Nine were excluded because they had no LN or NPSLE. Six suffered from LN, and one patient had NPSLE. All LN patients received BEL in addition to standard therapy including glucocorticoids, hydroxychloroquine, and mycophenolate mofetil in five cases, and tacrolimus in one case. Three patients with proteinuria >1,000 mg/g creatinine responded well (one complete, two partial renal responses); all other patients had decreasing proteinuria and a reduction in anti-dsDNA levels. The patient with NPSLE who had failed previous therapies had persistent clinical improvement of cutaneous and neuropsychiatric manifestations. There was one mild allergic reaction and one lower respiratory tract infection, but no other adverse events. One patient discontinued therapy due to a lack of improvement in clinical symptoms, another because of clinical remission.

Conclusions: In our series, BEL led to a decrease of proteinuria in patients with proteinuria of more than 1,000 mg/g creatinine despite standard of care treatment, and led to a marked clinical improvement in one patient with NPSLE. No adverse events were observed. Routinely administered BEL shows clinical efficacy on non-approved manifestations, but careful patient selection is warranted.

Keywords: systemic lupus erythematosus, lupus nephritis, neuropsychiatric lupus erythematosus, belimumab, monoclonal antibodies

INTRODUCTION

Systemic lupus erythematosus (SLE) is a rare autoimmune disease that can potentially affect every organ system (1). Many organ manifestations can be managed effectively with the available immunosuppressive therapies. Lupus nephritis (LN) and neuropsychiatric lupus erythematosus (NPSLE), however, are two of the organ manifestations that may lead to a worse overall prognosis
Belimumab (BEL) is a monoclonal antibody targeting B-lymphocyte stimulator (BLyS), and is FDA-approved as an additional treatment for SLE patients with persisting disease activity despite standard of care (SoC). It was investigated in the BLISS-52 and –76 trials (7, 8) and subsequently approved internationally; however, as LN and NPSLE were exclusion criteria in these trials, affected patients were only assessed indirectly (9). It is, therefore, as yet unclear whether or not BEL is of benefit for SLE patients with LN or NPSLE. Here, we aim to assess BEL's efficacy on LN and NPSLE patients who received BEL as in label-treatment, and report our experience using BEL in these off-label manifestations.

**RESULTS**

Of a total number of 16 patients with SLE treated with BEL at our center, nine were excluded due to absent LN or NPSLE. Of the remaining seven patients, six had biopsy-proven LN, and one had a clinically definite diagnosis of NPSLE.

**Effect on Lupus Nephritis**

The six patients with LN receiving BEL were all female and between 27 and 52 years of age. All had biopsy-proven LN class III, IV, or V, and a positive antibody status for anti-nuclear antibodies (ANA) and anti-ds DNA antibodies (Table 1). All patients received BEL intravenously and were followed up at regular intervals. Data collected three and six months after the initiation of BEL therapy are presented in Table 1.

**Case #1**

This 49-year-old patient of Asian ancestry had severe proteinuria of more than 4,000 mg/g creatinine and received BEL in addition to treatment with glucocorticoids (GC), hydroxychloroquine (HCQ), and mycophenolate mofetil (MMF) starting 1 month after renal biopsy. She developed allergic symptoms (fever, erythematous rash), and BEL was discontinued; upon re-exposition, however, no further allergic symptoms have developed, and the patient continues BEL therapy. Proteinuria was markedly reduced during BEL treatment but remained >650 mg/g creatinine after 6 months. She had a partial renal response.

**Case #2**

This 52-year-old Caucasian patient had undergone a renal transplant for LN almost 13 years before the initiation of BEL, and developed transplant kidney LN. Her background therapy consisted of GC, HCQ, leflunomide (LEF), and tacrolimus (TAC), the latter as part of her post-transplant immunosuppression. With BEL, the patient had mild improvement of proteinuria and clinically stable disease, but no additional benefit. Therefore, BEL and LEF were discontinued after five months as per the patient's wishes. It has to be noted, however, that the patient did not have significant proteinuria at the initiation of BEL.
### TABLE 1 | Clinical and laboratory characteristics of the study population.

| Patient | Age, sex, ethnicity | Disease duration (years) | Antibodies, complement levels | Renal biopsy (time before BEL initiation) | LN class | Previous therapies | Proteinuria (mg/g creatinine) (Baseline, after 6 months [% reduction]) | Current therapy | GC (mg/d) (Baseline, after 6 months [% reduction]) |
|---------|---------------------|--------------------------|------------------------------|----------------------------------------|----------|-------------------|---------------------------------------------------------------|----------------|-----------------------------------------------|
| 1       | 49, f, Asian        | 15                       | ANA+, dsDNA+, SSA+, SSB+, Histone+, C3↓, C4↓ | 1 month | IV–G | GC, CYC, HCQ, MMF | 4,074, 1202 (−70.5%) | GC, MMF       | 50, 2.5 (−95%)                                   |
| 2       | 52, f, Caucasian    | 19                       | ANA+, dsDNA+                | 12.5 years | V–IV | GC, HCQ, TAC | 117, 76 (−35.04%) | GC, HCQ, TAC | 5, 5 (0%)                                   |
| 3       | 30, f, Caucasian    | 4                        | ANA+, dsDNA+, SSA+, SSB+, Histone+, C3↓, C4↓ | 4 months | IV–G (A) | GC, HCQ, MMF | 346, 162 (−53.18%) | GC, HCQ, MMF | 60, 4 (−93.3%)                           |
| 4       | 27, f, Caucasian    | 8                        | ANA+, dsDNA+, C3↓            | 13 months | III (A, C) | GC, HCQ, MMF | 489, 115 (−76.48%) | GC, HCQ, MMF | 6.5, 5 (−15.3%)                             |
| 5       | 35, f, Caucasian    | 4                        | ANA+, dsDNA+, Histone+, C3↓, C4↓ | 4 months | III A | GC, MMF       | 159, 74 (−53.46%) | GC, AZA, HCQ | 15, 5 (−66.3%)                             |
| 6       | 40, f, Caucasian    | 17                       | ANA+, dsDNA+, APLA+         | 2 months | IV | GC, CYC, AZA, MMF | 4,420, 121 (−97.26%) | GC, MMF       | 15, 5 (−66.6%)                             |
| 7       | 75, m, Caucasian    | 19                       | ANA+, dsDNA+, U1snRNP+, Histone+, C3↓, C4↓ | 17 years | None | GC, CYC, AZA, MTX, RTX | 1,783, 655 (−63.26%) | GC, AZA       | 20, 2.5 (−87.5%)                          |

ANA, antinuclear antibody; APLA, anti-phospholipid antibodies; AZA, azathioprine; C3/4, complement factor 3/4; CYC, cyclophosphamide; dsDNA, double-stranded DNA; f, female; GC, glucocorticoids; HCQ, hydroxychloroquine; LN, lupus nephritis; m, male; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; TAC, tacrolimus.

**Case #3**
This further Caucasian patient, 30 years of age, received BEL in addition to GC/MMF/HCQ for relapsing arthritis and malar rash four months after her renal biopsy. A further reduction by about 50% after six months of treatment could be demonstrated (Table 1). She was also able to taper down her steroid dosage and experienced overall improvement of her quality of life.

**Case #4**
This 27-year-old patient received BEL in addition to GC, HCQ and MMF starting 13 months after renal biopsy and was shown to have a significant albeit less pronounced reduction in proteinuria (−35%, Table 1). She experienced a clinical remission of SLE and wished to discontinue the additional treatment later on.

**Case #5**
This 35-year-old Caucasian patient received BEL in addition to GC/MMF for persisting skin disease and arthritis starting four months after renal biopsy. She exhibited another significant reduction in proteinuria of 53% after six months. She was also able to reduce her GC doses and reported an overall improvement of quality of life.

**Case #6**
This patient had undergone multiple treatment regimens, including azathioprine (AZA) and cyclophosphamide (CYC) for severe LN class IV with high-grade proteinuria and stage 4 chronic kidney disease. She had experienced multiple infectious complications requiring antibiotic therapy. Her background regimen consisted of GC and MMF when BEL was initiated two months after her most recent renal biopsy. She had a significant reduction in proteinuria from >4,000 mg/g creatinine to just over 100 mg/g creatinine. In light of further respiratory and urinary tract infections, the dose was reduced, and the administration of BEL was switched from intravenous to subcutaneous application. The patient continued to benefit from BEL therapy and has remained on the treatment for over two years.

**Case #7—Effect on Neuropsychiatric Lupus**
The patient with NPSLE is a Caucasian gentleman with a diagnosis of SLE at the age of 56 and presented with multi-organ involvement including skin erythema and ulcerations, arthralgia,
myalgia, bicytopenia, and pulmonary fibrosis with subsequent pulmonary arterial hypertension. During a flare in 2016, he had developed cerebral manifestations with dysarthria, severe immobilizing ataxia, and concentration deficits. The patient failed or could not tolerate multiple therapies, including HCQ, CYC, MMF, LEF, and AZA, as well as rituximab (RTX) so that the cutaneous and neuropsychiatric disease manifestations remained insufficiently controlled. Therefore, we decided to...
initiate treatment with BEL, which was given in conjunction with three doses of methylprednisone (250 mg) and rapidly tapered down. After three intravenous infusions with BEL the cutaneous and, most importantly, neuropsychiatric symptoms (dysarthria and ataxia) improved markedly, enabling the patient to continue a largely independent lifestyle with minimal assistance. Also, findings on cerebral magnetic resonance imaging (MRI) stabilized over time (Figure 2). Additionally, this patient also had proteinuria, but he did not have biopsy-proven LN. His first renal biopsy was performed 17 years before BEL initiation. Later on, we performed another renal biopsy in this patient due to increasing proteinuria, which showed focal segmental glomerulosclerosis unrelated to SLE.

DISCUSSION

Of the seven patients analyzed in this study, all showed significantly reduced levels of proteinuria during treatment with BEL, ranging from $-35 \text{ to } -97\%$. The levels of anti-dsDNA antibodies remained stable or diminished further with SoC plus BEL. Complement levels showed a tendency to normalize. Perhaps most importantly, all patients were able to significantly reduce the glucocorticoid doses and reported a symptomatic improvement of quality of life, although we did not formally assess this with questionnaires. In a recent analysis of the MAINTAIN nephritis trial, cut-off values below 650 mg/d after 6 months and 700 mg/d after 12 months were associated with a more favorable renal prognosis (11). Therefore, it should be highlighted that four out of the seven patients analyzed had a proteinuria of $<500 \text{ mg/g creatinine}$, which would be considered as complete renal remission of LN, and, therefore, not prompt an escalation of immunosuppressive therapy. We did, however, include these patients in our analysis as they had biopsy-proven LN and were given BEL for continued disease activity, which might affect their renal outcome in the long run. Another limitation of the study might be that we routinely measure proteinuria in spot urine samples in an outpatient setting. This has been shown to be a reliable alternative (12). In a meta-analysis comparing spot urine to 24-h urine collection, it was argued that both tests correlated, at best, moderately (13). These findings are limited by the fact that only three of the 13 analyzed studies used Bland-Altman analysis as appropriate test for agreement between these two different methods.

The patient with NPSLE experienced a remarkable clinical improvement that allowed him to continue a mostly independent lifestyle. It has to be noted that imaging findings do not always correlate with clinical findings in NPSLE, as MRI lesions may be found in asymptomatic patients (14).

Adjunct therapy with BEL in patients with LN or NPSLE remains off-label: According to the EULAR 2019 standard of care recommendations for LN (15), BEL should currently be considered in patients with extrarenal lupus manifestations with poor or no response to first-line treatment.

While the results of further prospective clinical trials are eagerly awaited, a post-hoc analysis of the available BLISS trial data of patients with renal manifestations at baseline concluded in favor of BEL (16). Broadening this retrospective data pool to include patients with LN beyond the BLISS trials led to the conclusion that 55.1% of LN patients showed an improvement in renal parameters with BEL, including a reduction in proteinuria of 38% (9).

Interestingly, multiple case reports have been published suggesting a benefit of BEL in patients with LN, both as an adjunct treatment when first- and/or second-line therapies have failed (17–19), and as maintenance therapy after RTX (20–22). A case in which LN was refractory to RTX and then successfully treated with BEL has also been reported (23).

On the other hand, caution has been raised by some authors who witnessed patients developing LN while undergoing therapy with BEL (24, 25). However, a recent extensive review (26) of the treatment of refractory LN concludes that BEL—in combination with RTX, and possibly as monotherapy—will play a role. In the meantime, Glaxo Smith Kline, the manufacturer of Belimumab, has released a news outline that the phase 3 study of BEL in LN reached its primary endpoint (27). The final results have not been published as of yet but are awaited eagerly.

As far as NPSLE itself is concerned, data and case reports are not available. BLyS has, however, been shown to be elevated in the cerebrospinal fluid of NPSLE patients, making it a feasible target (28). A concise review of the available evidence (29) concluded that while, again, the BLISS trials were neither designed nor powered for NPSLE research, BEL appears to have been beneficial for neuropsychiatric symptoms.

In conclusion, the data of our retrospective series of seven cases presented in this study show a favorable effect of BEL on proteinuria in patients with biopsy-proven lupus nephritis as well as on neuropsychiatric manifestations in one patient with severe NPSLE. While further randomized controlled trials and subsequent recommendations concerning these indications are awaited, this data may help other clinicians to find appropriate and safe treatment for their patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the University Medical Center Göttingen. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.
AUTHOR CONTRIBUTIONS

MP treated patients, collected and analyzed data, created figures, and co-wrote the manuscript. BT analyzed data, created figures, and reviewed the manuscript. NN collected data and reviewed the manuscript critically. GM treated patients, analyzed data, and reviewed the manuscript. PK treated patients, conceived the study, collected and analyzed data, created figures, and co-wrote the manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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