Concise report

De novo lupus nephritis during treatment with belimumab

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Abstract

Objective. In light of reports of de novo LN during belimumab (BLM) treatment, we sought to determine its frequency and contributing or protective factors in a real-life setting.

Methods. Patients with SLE who received BLM between 2011 and 2017 at five European academic practices were enrolled (n=95) and followed longitudinally for a median time of 13.1 months [interquartile range (IQR): 6.0–34.7]; 52.6% were anti-dsDNA positive, 60.0% had low complement levels, and 69.5% had no renal involvement prior to/at BLM initiation [mean disease duration at baseline: 11.4 (9.3) years]. Age- and sex-matched patients with non-renal SLE who had similar serological profiles, but were not exposed to BLM, served as controls (median follow-up: 132.0 months; IQR: 98.3–151.2).

Results. We observed 6/66 cases (9.1%) of biopsy-proven de novo LN (4/6 proliferative) among the non-renal BLM-treated SLE cases after a follow-up of 7.4 months (IQR: 2.7–22.2). Among controls, 2/66 cases (3.0%) of de novo LN (both proliferative) were observed after 21 and 50 months. BLM treatment was associated with an increased frequency and/or shorter time to de novo LN [hazard ratio (HR): 10.7; 95% CI: 1.7, 67.9; P=0.012], while concomitant use of antimalarial agents along with BLM showed an opposing association (HR: 0.2; 95% CI: 0.03, 0.97; P=0.046).

Conclusion. Addition of BLM to standard-of-care did not prevent LN in patients with active non-renal SLE, but a favourable effect of concomitant use of antimalarial agents was implicated. Studies of whether effects of B-cell activating factor inhibition on lymphocyte subsets contribute to LN susceptibility are warranted.

Key words: SLE, LN, belimumab, autoantibodies, complement, biologic agents, treatment, adverse events

Introduction

SLE is a chronic, multisystem autoimmune disease with unmet needs, such as delayed diagnosis, premature atherosclerosis, drug-associated organ damage and a prominent impairment of health-related quality of life [1]. The wide range of manifestations and serological findings pose challenges with regard to diagnosis and treatment. Today, standard-of-care (SoC) therapy includes glucocorticoids, antimalarials, immunosuppressants and biologic agents, e.g. belimumab (BLM) and rituximab (RTX). The selection of drugs is mainly based on the
afflicted organ systems and the organ-specific or global disease activity [2]. LN is a manifestation of SLE with a potentially life-threatening course [3].

BLM is a recombinant human IgG1-λ monoclonal antibody that specifically binds the soluble form of B cell activating factor (BAFF). The efficacy of BLM has been demonstrated to date in five placebo-controlled phase III trials and several observational studies [4]. Although post hoc analysis of clinical trials of BLM showed superiority of BLM over placebo in preventing renal flares [5] and a systematic review suggested an overall promising effect of BAFF inhibition on renal outcomes [6], development of LN during BLM treatment has also been reported [7–10]. Clinical trials of BLM in LN, either as an add-on therapy to SoC or in combination with RTX, are underway [11–13] and the BLISS-LN trial recently demonstrated superiority of addition of BLM to SoC for active LN over SoC alone [14].

We herein report cases of de novo LN during treatment with BLM observed in our academic practices, and cases of LN flares in patients with a history of renal SLE at the time of BLM initiation. We further aimed at identifying factors or risk phenotypes that are associated with the development of LN, in order to contribute to optimized monitoring during treatment with BLM.

Methods

Patients

Patients, classified with SLE according to the 1982 ACR [15] and/or 2012 SLICC [16] criteria, receiving BLM 10 mg/kg intravenously at week 0, 2, 4 and thereafter every fourth week from its approval in 2011 until 31 December 2017 in the Day Care Units of four Swedish academic rheumatology centres (Linköping, Lund, Stockholm and Uppsala) and one academic centre in Leeds, UK, were followed longitudinally within the frame of observational research programmes, and were included in the present report (n = 95). BLM was given as an add-on to background SoC, with no change in SoC implemented unless clinically indicated. None of these patients were given cyclophosphamide, RTX or other B cell depleting agents during treatment with BLM. No patient selection was applied other than clinical indication. None of the patients had a history of renal involvement before BLM initiation. As a comparator group to the non-renal SLE cases exposed to BLM, we included 66 non-renal SLE cases from Linköping and Stockholm, individually matched for age and sex, with similar serological profiles (anti-dsDNA positivity, low complement protein 3 and/or 4), who were also followed longitudinally; no selection other than matched serology and age at baseline was applied. Kidney biopsy was performed in the case of a suspected new onset of LN during follow-up. Patient characteristics are detailed in Table 1.

Definitions

We defined de novo LN as a new onset of significant proteinuria, defined as a urinary protein-to-creatinine ratio or protein excretion in 24-h urine collection corresponding to >0.5 g/day, combined with renal histology consistent with LN according to the WHO and/or 2003 International Society of Nephrology/Renal Pathology Society classification [17], in patients who previously had not met the ACR criterion for renal disorder [15].

Global SLE disease activity was evaluated using the SLEDAI-2K [18], and organ damage using the SLICC/ACR Damage Index (SDI) [19]. For SLEDAI-2K scores, laboratory and serological items were assessed based on results from routine tests at the local university hospital laboratories.

Statistics

Comparisons between matched non-renal SLE patients who received BLM vs those who did not were performed using Wilcoxon’s signed rank test for continuous and McNemar’s test for dichotomous variables. The occurrence of de novo LN or LN flares during follow-up was illustrated using Kaplan–Meier curves, and the pairwise log-rank (Mantel–Cox) test was employed to compare the de novo LN distributions between BLM exposed vs not exposed non-renal SLE patients. Contingency between unrelated dichotomous variables was tested using Fisher’s exact test. Proportional hazards (Cox) regression was used to investigate factors and disease phenotypes associated with LN development during therapy. P-values <0.05 were considered statistically significant. IBM SPSS version 25 software (IBM Corp., Armonk, NY, USA) was used for statistical analyses and GraphPad Prism 7 (GraphPad Software Inc., La Jolla, CA, USA) for construction of graphs.

Ethical considerations

The study complied with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. The study protocol was approved by regional ethics review boards.

Results

Outcome of cases without prior LN

As shown in Table 1, non-renal SLE patients who were selected for treatment with BLM had comparable serological profiles, disease duration and SDI scores but higher baseline SLEDAI-2K scores (mean (s.d.): 8.2 (4.7)) than age- and sex-matched non-renal SLE controls (4.9 (3.7); P < 0.001). Accordingly, they were on higher daily prednisolone doses (11.1 (9.4) mg vs 7.3 (12.1) mg; P = 0.004) and a higher proportion within BLM-treated non-renal SLE patients used immunosuppressants (60.6%) compared with the controls (31.8%; P = 0.002), but the proportions of patients using antimalarial agents did not differ significantly (P = 0.137). Use of
immunosuppressants and antimalarials for the controls during the entire follow-up period is delineated in Supplementary Figs S1 and S2 (available at Rheumatology online), respectively.

Six patients (9.1%) developed a biopsy-proven de novo LN in the BLM-treated non-renal SLE group after a median follow-up time of 7.4 (IQR: 2.7–22.2) months. Among the comparators, two individuals (3.0%) developed de novo LN, one class III and one class IV after 21 and 50 months, respectively.

TABLE 1 Patient characteristics

| Item                                      | Belimumab-treated SLE | Non-renal SLE comparators | P-value |
|-------------------------------------------|-----------------------|---------------------------|---------|
|                                           | Total | Non-renal | P-value |
| **Background variables**                  |       |           |         |
| Number of cases, n                        | 95    | 66        | 66      |         |
| Age, mean (s.d.), years                   | 42.2 (14.2) | 42.2 (15.2) | 43.4 (16.0) | 0.152 |
| Females, n (%)                            | 89 (93.7) | 63 (95.5) | 63 (95.5) | NA     |
| Current tobacco smoking, n (%)            | 11 (12.5); n = 88 | 9 (15.0); n = 60 | 14 (21.2) | 0.367 |
| Former tobacco smoking, n (%)             | 25 (28.4); n = 88 | 14 (23.3); n = 60 | 23 (34.8) | 0.047 |
| Caucasian, n (%)                          | 86 (90.5) | 59 (89.4) | 64 (97.0) | NA     |
| African, n (%)                            | 6 (6.3) | 5 (7.6) | 0 (0.0) | NA     |
| Asian, n (%)                              | 2 (2.1) | 2 (3.0) | 2 (3.0) | NA     |
| Hispanic, n (%)                           | 1 (1.1) | 0 (0.0) | 0 (0.0) | NA     |
| Diabetes until enrolment, n (%)           | 3 (3.2) | 0 (0.0) | 0 (0.0) | NA     |
| Hypertension until enrolment, n (%)       | 23 (24.2) | 9 (13.6) | 14 (21.2) | 0.332 |
| **Disease variables at enrolment**        |       |           |         |
| Duration of SLE, mean (s.d.), years       | 11.4 (9.3) | 10.5 (9.1) | 9.8 (11.1) | 0.529 |
| SLEDAI-2K score, mean (s.d.)              | 9.3 (5.9) | 8.2 (4.7) | 4.9 (3.7) | <0.001 |
| SDI score, median (IQR)                   | 1 (0–1); n = 93 | 0 (0–1); n = 64 | 0 (0–2) | 0.594 |
| Serological activity<sup>a</sup>, n (%)   | 68 (71.6) | 47 (71.2) | 50 (75.8) | 0.250 |
| Anti-dsDNA positive, n (%)                | 50 (52.6) | 33 (50.0) | 34 (51.5) | 1.000 |
| Low complement, n (%)                     | 57 (60.0) | 40 (60.6) | 41 (62.1) | 1.000 |
| Anti-Smith positive, n (%)                | 24 (25.3) | 16 (24.2) | 21 (32.8) | 0.832 |
| **Main reasons for belimumab**            |       |           |         |
| General, n (%)                            | 4 (4.2) | 3 (4.5) | NA | NA |
| Mucocutaneous, n (%)                      | 55 (57.9) | 39 (59.1) | NA | NA |
| Musculoskeletal, n (%)                    | 54 (56.8) | 39 (59.1) | NA | NA |
| Haematological, n (%)                     | 12 (12.6) | 8 (12.1) | NA | NA |
| Cardiorespiratory, n (%)                  | 6 (6.3) | 4 (6.1) | NA | NA |
| Renal, n (%)                              | 9 (9.5) | 0 (0.0) | NA | NA |
| Neurological, n (%)                       | 5 (9.5) | 2 (3.0) | NA | NA |
| Immunological, n (%)                      | 3 (3.2) | 2 (3.0) | NA | NA |
| **Ongoing concomitant treatments**        |       |           |         |
| Daily prednisolone dose<sup>b</sup>, mean (s.d.), mg | 11.3 (9.4) | 11.1 (9.4) | 7.3 (12.1)<sup>a</sup> | 0.004 |
| Antimalarial agents, n (%)                | 67 (70.5) | 45 (68.2) | 36 (54.5) | 0.137 |
| Immunosuppressants<sup>c</sup>, n (%)     | 58 (61.1) | 40 (60.6) | 21 (31.8) | 0.002 |
| Azathioprine, n (%)                       | 27 (28.4) | 17 (25.8) | 8 (9.1) | 0.013 |
| Methotrexate, n (%)                       | 14 (14.7) | 11 (16.7) | 8 (12.1) | 0.629 |
| Mycophenolate mofetil/sodium, n (%)       | 14 (14.7) | 11 (16.7) | 3 (4.5) | 0.057 |
| Other immunosuppressants, n (%)           | 4 (6.8) | 2 (3.0) | 5 (7.6) | 0.375 |

In cases of missing values, the total number of available observations (n) is indicated. P-values are derived from comparisons between non-renal SLE patients who were treated with belimumab and individually matched for age and sex non-renal SLE comparators who were not treated with belimumab, using Wilcoxon’s signed rank test for continues variables and McNemar’s test for dichotomous variables, or the χ² test in cases of missing values in one of the two groups. Significant P-values are indicated in bold. <sup>a</sup>Anti-dsDNA positivity and/or low complement levels. <sup>b</sup>At the time of belimumab initiation or enrolment for the comparators. <sup>c</sup>Excluding antimalarial agents. <sup>d</sup>Median (IQR): 6.4 (0.5–13.4) years. <sup>e</sup>Median (IQR): 5.0 (0.0–10.0) mg. IQR: interquartile range; NA: not applicable or not available; SDI: SLICC/ACR Damage Index.

In the six patients who developed de novo LN, all Caucasians, BLM was primarily initiated for active mucocutaneous and/or musculoskeletal disease. All had positive anti-dsDNA levels and were hypocomplementaemic at baseline. At BLM initiation, SLEDAI-2K scores ranged from 6 to 23, and the daily prednisolone dose from 7.5 to 30 mg. Only 2/6 patients were on concomitant treatment with antimalarials. The renal histopathology in 4/6 subjects was consistent with proliferative LN (class III or IV), whereas the two remaining cases...
showed membranous LN (class V) in combination with class II. Detailed information is shown in Supplementary Table S1, available at Rheumatology online.

As illustrated in Fig. 1A, non-renal SLE patients treated with BLM showed a higher frequency of and/or shorter time to de novo LN compared with non-renal SLE patients who did not receive BLM (hazard ratio (HR): 10.7; 95% CI: 1.7, 67.9; \(P=0.012\)). This association between BLM treatment and de novo LN development remained significant after adjustment for SLEDAI-2K scores (HR: 8.3; 95% CI: 1.2, 57.0; \(P=0.031\)), while no such association was seen for SLEDAI-2K scores as a co-variate in the same model (HR: 1.1; 95% CI: 0.9, 1.2; \(P=0.362\)). The Kaplan–Meier curve in Fig. 1B illustrates the course of BLM-treated patients with and without a history of renal SLE at BLM initiation, as well as the non-renal comparators, until the time of LN development or the last available evaluation.

Next, we selected patients not exposed to BLM with baseline SLEDAI-2K scores >4, which yielded a control group with comparable SLEDAI-2K scores [8.5(3.2); \(n=25\)] to the non-renal BLM group. None of the patients within this group had developed LN after a mean follow-up of 126.5 (37.8) months.

Outcome of cases with previous LN

Among the 29/95 BLM-treated patients with LN prior to enrolment, but quiescent renal disease at the time of BLM initiation, two cases (6.9%) of LN flare were observed after 1 and 9 months (Fig. 1B). One of these patients underwent a renal biopsy that showed a proliferative LN (class IV); prior to BLM treatment, this patient had a history of class IV nephritis that later shifted to class V in two subsequent biopsies. The second patient presented with heavy proteinuria, haematuria and hypertension, indicating renal flare. Therefore, a clinical decision was made not to wait for a biopsy and instead to promptly initiate induction therapy with pulsed cyclophosphamide.

Associations between anti-dsDNA seroconversion and LN development

Of patients with positive anti-dsDNA levels at baseline and available follow-up data, no seroconversion was observed among those who developed LN (\(n=8\)) in the BLM-treated group (\(n=46\)) or de novo LN (\(n=6\)) in the BLM-treated non-renal SLE group (\(n=30\)), while 15 and 13 patients seroconverted among those who did not develop LN (\(n=38\); \(P=0.040\)) or de novo LN (\(n=24\); \(P=0.024\)), respectively. Of patients with low complement levels at baseline, one among those who developed de novo LN showed normalization during follow-up; no significant association between C3/C4 normalization and LN development was observed.

Predictors of LN development

The following variables were investigated using univariable Cox regression analysis: age at baseline, SLE disease duration, baseline SLEDAI-2K score, anti-
dsDNA positivity, low complement (C3 and/or C4), serological activity (anti-dsDNA positivity and/or hypocomplementaemia), anti-Smith positivity, SDI score, current or former tobacco smoking, daily prednisolone dose, use of antimalarial agents, comitant use of immunosuppressants, comorbid hypertension and diabetes, and history of renal involvement when all BLM-treated cases were analysed. From these variables, only use of antimalarial agents was negatively associated with development of LN when all BLM-treated patients were considered (coefficient: −0.6; HR: 0.2; 95% CI: 0.05, 0.86; P = 0.031) and with de novo LN when non-renal cases were considered (coefficient: −1.7; HR: 0.2; 95% CI: 0.03, 0.97; P = 0.046).

Discussion

In our real-life setting of BLM-treated subjects, 9% of patients with no renal history developed de novo LN and 7% of patients with prior LN relapsed during treatment. Using age- and sex-matched non-renal comparators with similar serological profiles and a long follow-up, we showed that use of BLM was associated with an increased frequency of de novo LN. Interestingly, our data indicated that concomitant use of antimalarial agents along with BLM may be protective.

In 2014, de novo LN during BLM treatment was first reported in a serologically active middle-aged woman with relapsing serositis, resistant to conventional therapies, and unacceptable doses of corticosteroids [7]. Later, three patients who developed LN over the first year of BLM therapy were observed among 195 patients in 10 centres, mainly American [8]. Staveri et al. reported de novo LN shortly after BLM initiation in two women who had a moderately active non-renal SLE at baseline; one was anti-dsDNA negative [9]. Finally, one case of de novo LN was observed among 23 patients (4%) treated with BLM in a Spanish setting [10].

It is important to highlight that the majority of patients chosen for biologic therapy had a severe disease course, and had failed conventional disease-modifying non-biologic drugs, including the patients who developed de novo LN, of whom 5/6 had a long-standing disease (>7 years). A possible explanation for the development of de novo LN might be a more aggressive disease, as reflected by higher SLEDAI-2K scores and prednisolone doses in these patients; however, neither these features nor SDI scores, also a proxy for severe disease course, were associated with LN development. The non-renal SLE comparators were carefully selected to have similar serological profiles and age at enrolment, and were individually matched with the BLM-treated non-renal SLE patients. However, they had lower levels of disease activity, lower prednisolone doses and fewer patients required immunosuppressants. This reflects that the majority of patients in the comparator group were in a quiescent phase of their disease at the time of enrolment, but could also mirror an overall milder disease phenotype. Nevertheless, they were followed for a longer time compared with the BLM-treated patients, and the observed association between BLM and de novo LN was still present after adjustment for disease activity. Notably, in a subgroup of the comparators comprising 25 patients with comparable degree of activity to the BLM-treated group, none developed de novo LN during follow-up. The reasons behind the observed associations are not clear. Awareness of the steroid-sparing effects of belimumab may have contributed to rapid tapering of glucocorticoid doses, which in turn unveiled renal activity. Belimumab binds to the soluble counterpart of BAFF, a molecule implicated in the pathogenesis of LN [20, 21], and has been shown to alter absolute and relative numbers of B cell subsets, mainly B cells of early developmental stages [22, 23]. However, the long-term consequences of BAFF inhibition, e.g. regarding B cell subsets with regulatory properties, have yet to be determined. Such long-term effects on subsets of B cells could potentially increase the susceptibility of these patients to develop a more severe or organ-specific (renal) phenotype. Accumulating evidence indicates that B cells exert regulatory properties through production of IL-10 [24]. Hence, our recent observation of decreasing serum IL-10 levels during BLM treatment [25] may be suggestive of a regulatory B cell downregulation, collectively warranting granular survey of BLM-mediated effects on the B cell repertoire.

Another interesting finding was that concomitant use of antimalarial agents along with BLM was implied to be protective against the development of de novo LN or LN relapse. Although no firm conclusions can be drawn due to the relatively low number of patients and the known non-adherence of patients to antimalarials, this association is in line with the known beneficial effects of antimalarials that include prevention of renal flares [26] and is also of particular importance in light of a recent report that showed that decreasing levels of IgG and IgA anticyclic-antibodies in BLM-treated patients were solely observed among those receiving antimalarials [27]. The mechanistic explanation for such a synergy remains to be elucidated. SLE patients using antimalarials have been shown to have lower BAFF levels compared with non-users [28]; while BLM binds to circulating BAFF, antimalarials are likely to hamper type I IFN-mediated BAFF excretion, potentially contributing to additive neutralization. Furthermore, antimalarials also bind nucleic acids, impeding Toll-like receptor activation and therefore innate immune responses, and inhibit loading of antigen into MHC and antigen presentation to T cells, both constituting further explanations for the additional benefit in patients in whom B cells are inhibited [29].

The observational design of our study constituted a limitation, yet the cases represent real-life use of BLM in our academic practices. The vast majority of study participants were of Caucasian origin, reflecting the patient population in Sweden and the UK, and the
findings cannot be directly extrapolated to other populations, in particular African/African American or Asian patients. Another limitation was the relatively low number of patients who were enrolled and those who developed de novo LN and LN relapse, limiting the power in statistical analyses. Lastly, non-adherence assessment for background therapies was not performed.

Although firm conclusions cannot be drawn, our observations imply that BLM may not be sufficient for the prevention of LN and suggest close monitoring of BLM-treated patients for signs of evolving renal disease. Concomitant use of antimalarial agents may exert synergistic effects along with BLM with regard to renal outcomes, a finding that warrants corroboration in other settings. Investigation of the long-term effects of BAFF inhibition on B cell subsets with regulatory properties is merited.

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Data availability statement

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at Rheumatology online.

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