Patient Related Outcome Measures

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REVIEW

Impact of Belimumab on Patient-Reported Outcomes in Systemic Lupus Erythematosus: Insights from Clinical Trials and Real-World Evidence

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Abstract: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease, characterised by a relapsing-remitting pattern of inflammatory activity, with each relapse contributing to irreversible end-organ damage with detrimental effects on patients' course, adding up to morbidity burden and shortening life-length. Along with several other demographic, socioeconomic, and life-style factors, high inflammatory activity and accrued organ damage have been coupled with adverse health-related quality of life (HRQoL) within physical, mental, and psychosocial aspects. The management of SLE has improved substantially during the last decades, owing to a technological explosion that has advanced drug development towards more targeted options. Being the first drug to be approved for SLE in more than half a century and the first in history biological agent for SLE, the introduction in 2011 of the monoclonal antibody belimumab that specifically binds to the soluble counterpart of B cell activating factor (BAFF) was a breakthrough in SLE drug development. The efficacy and favourable safety profile of belimumab has been demonstrated across several clinical trials and observational studies. Herein, we reviewed the literature and provide a summary on the effects of belimumab on SLE patients' HRQoL based on 23 studies. Belimumab has been shown to induce clinically important improvements in physical aspects of HRQoL and in fatigue, the latter being a common and major complaint within the SLE population. People with SLE overall benefit more from belimumab within physical compared with mental aspects of HRQoL. However, despite improvements of clinical and immunological features upon therapy with belimumab, HRQoL perception remains unsatisfactory for a substantial percentage of the patients. Finally, our review made apparent an urgent need for optimisation of the use of patient-reported outcome measures, both in research and clinical practice.

Keywords: systemic lupus erythematosus, health-related quality of life, fatigue, patient-reported outcomes, belimumab, monoclonal antibodies

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic, autoimmune disease that is characterised by a relapsing-remitting pattern of inflammatory activity, with each relapse contributing to irreversible end-organ damage.[1] Such damage has detrimental effects on SLE patients' course, adding up to morbidity burden and shortening life-length.[2,3] Along with several other demographic, socioeconomic, and life-style factors, high inflammatory activity and accrued organ damage have been coupled with adverse health-related quality of life (HRQoL) within physical, mental, and psychosocial aspects.[4,5]

The management of SLE has improved substantially during the last decades as a result of technological advances that have propelled drug development towards more targeted options, such as biological agents.[6] Owing to the central role of B cells in SLE pathogenesis,[7] several compounds that target the B cell compartment have been investigated as candidate

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treatments of SLE.[8] Belimumab is one of those compounds; it is a fully human IgG1-λ monoclonal antibody that specifically binds to the soluble form of B cell activating factor belonging to the TNF family (BAFF; also known as B lymphocyte stimulator, BLyS). Being the first biological agent to be licensed for treating SLE and the first drug to be approved for SLE in more than half a century in 2011, the introduction of belimumab indicated a breakthrough in SLE drug development.

Belimumab was approved in 2011 for the treatment of adult patients with active SLE after two pivotal Phase III randomised clinical trials (RCTs), ie, the BLISS-52 and BLISS-76 trials.[9,10] The initial licence for belimumab was for its intravenous (IV) administration at a dose of 10 mg/kg every second week for four weeks, and every fourth week thereafter. Later, the subcutaneous (SC) administration at a weekly dose of 200 mg was added as an alternative option.[11] Belimumab has also received approval for use in paediatric SLE,[12] and since recently in lupus nephritis (LN).[13]

The efficacy and favourable safety profile of belimumab has been demonstrated across several clinical trials and observational studies.[9–24] Safety signals reported in the literature mainly comprise infusion reactions and non-severe infections.[9,10,15,21,22,25] Data from two RCTs[10,26] raised concerns about an increased risk for psychiatric events, including severe depression and suicidal ideation, but a systematic review and meta-analysis of 11 RCTs did not corroborate this risk.[27] Overall, belimumab has a satisfactory safety profile, also during long-term usage.[21,22]

A previous review summarised the impact of belimumab on patient-reported outcomes based on results from the phase III belimumab RCTs,[28] and we recently reviewed the effect of different biological agents on SLE patients' HRQoL, focusing on methodological approaches for reporting HRQoL outcomes.[29] We herein reviewed the literature and provide a summary on the effects of belimumab on SLE patients' HRQoL based on RCTs and real-world evidence, aiming to highlight clinical implications.

Methods

We searched the MEDLINE and EMBASE databases from database inception until March 2022. To increase sensitivity, a two-block search was conducted including the search terms "systemic lupus erythematosus" and "belimumab". The search strategy can be found as Supplementary Material. Interventional studies, including RCTs and their respective open-label extension studies and post-hoc analyses, quasi-experimental studies, cohort studies, and cross-sectional studies, were deemed eligible. Studies in languages other than English, Spanish, or Swedish (languages spoken by the authors) were excluded.

The patient perspective was obtained through contributions from a patient research partner (YE) at the level of study design and conduct.

Results

We identified 23 eligible articles of studies that comprised patients with SLE who were treated with belimumab (Figure 1). Table 1 summarises the characteristics of studies that were deemed eligible for analysis, while Table 2 details the effectiveness of belimumab in terms of HRQoL in the different studies. The most common instruments used to measure HRQoL were generic, particularly the Medical Outcomes Study Short Form 36 (SF-36) health survey,[30] the EuroQol 5-Dimension health questionnaire (EQ-5D),[31] and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale, the latter to specifically assess fatigue.[32]

The SF-36 health survey is a 36-item questionnaire that assesses self-perception of HRQoL over the past four weeks. Patient responses are computed and summarised into eight subscales that denote distinct HRQoL aspects, ie, physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), social functioning (SF), vitality (VT), role emotional (RE), and mental health (MH). Additionally, scores from these subscales are weighted and summarised into the physical component summary (PCS) and the mental component summary (MCS). Higher scores in SF-36 subscales and component summaries denote better HRQoL.

EQ-5D consists of a visual analogue scale (VAS) that captures overall health status, and a descriptive system that comprises five questions, each representing a distinct health dimension. Patient responses to these questions are summarised into a health profile, and an index score; the latter score is calculated based on population-specific valuation

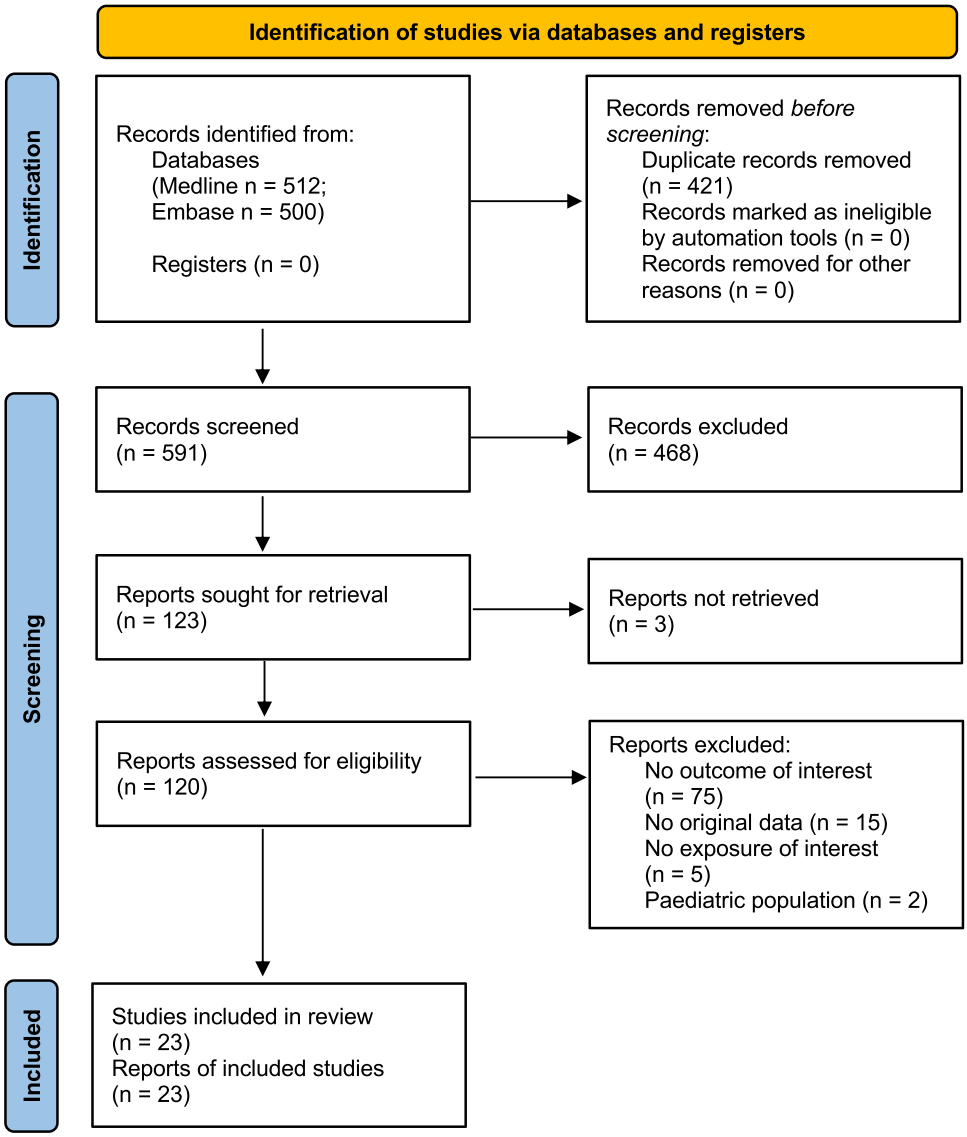

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71, Open Access.

sets and ranges from less than 0 to 1. An EQ-5D index score of 1 represents the desired perception of health status, and is termed full health state (FHS).[33]

FACIT-F is a 13-item survey that evaluates fatigue over the past seven days.[32] Patient responses are transformed into a score that ranges from 0 (maximal fatigue) to 52 (minimal fatigue).

Phase II RCT of Belimumab

In the phase II RCT of belimumab, SLE patients with moderate disease activity were randomly allocated to IV infusions of three doses of verum drug or placebo. The trial did not meet its primary efficacy endpoint; however, belimumab induced greater clinical benefits than placebo in seropositive patients and in patients who received prednisone >7.5 mg/day at baseline. Patients who received belimumab 10 mg/kg self-reported improvements in SF-36 PCS scores, which exceeded those considered clinically important and were greater than those reported by patients who received placebo (3.4 ± 0.8 versus 1.4 ± 0.7; $P < 0.05$); no such differences between belimumab and placebo were noted for the lower belimumab doses.[34]

Table 1 Characteristics of Eligible Studies on Belimumab in Patients with Systemic Lupus Erythematosus

Study	Setting	Study Groups	Follow-Up	N
Furie et al, 2008[57]	Phase I RCT	BLM 1, 4, 10 and 20 mg/kg IV Placebo	Up to 15 weeks	70
Wallace et al, 2009[34]	Phase II RCT	BLM 1, 4 and 10 mg/kg IV Placebo	52 weeks	449
BLISS-52 and BLISS-76 (Navarra et al, 2011, Furie et al 2011, Strand et al, 2014)[9,10,35]	Phase III RCTs, including post-hoc analyses	BLM 1 mg/kg IV BLM 10 mg/kg IV Placebo	BLISS-52: 52 weeks BLISS-76: 76 weeks	1684
BLISS-SC (Stohl et al, 2017)[11]	Phase III RCT	BLM 200 mg SC Placebo	52 weeks	836
Van Vollenhoven et al, 2012[14]	Post-hoc analysis of phase III RCTs	BLM 1 mg/kg IV BLM 10 mg/kg IV Placebo	BLISS-52: 52 weeks BLISS-76: 76 weeks	876
Doria et al, 2018[38]	Post-hoc analysis of phase III RCT	BLM 200 mg SC Placebo	52 weeks	356
Gomez et al, 2021[37]	Post-hoc analysis of phase III RCTs	BLM 1 mg/kg IV BLM 10 mg/kg IV Placebo	BLISS-52: 52 weeks BLISS-76: 76 weeks	760
Borg et al, 2021[39]	Post-hoc analysis of phase III RCTs	BLM 1 mg/kg IV BLM 10 mg/kg IV Placebo	BLISS-52: 52 weeks BLISS-76: 76 weeks	1684
Lindblom et al, 2021[36]	Post-hoc analysis of phase III RCTs	BLM 1 mg/kg IV BLM 10 mg/kg IV Placebo	BLISS-52: 52 weeks BLISS-76: 76 weeks	1665
Maslen et al, 2021[58]	Post-hoc analysis of phase III RCTs	BLM 10 mg/kg IV BLM 200 mg SC Placebo	BLISS-52 and -SC: 52 weeks BLISS-76: 76 weeks	969
BEL 112233 (Strand et al, 2019)[41]	Phase III RCTs OL extension	BLM 10 mg/kg IV	Up to 6 years	268
Swedish cohort (Parodis et al, 2017)[15]	Prospective cohort	BLM 10 mg/kg IV	Up to 53 months	58
Swedish cohort (Parodis et al, 2019)[16]	Prospective cohort	BLM 10mg/kg IV	Up to 24 months	34
Italian cohort (Gatto et al, 2020)[22]	Retrospective cohort	BLM 10mg/kg IV	Up to 48 months	466
OBSErve Germany (Schwarting et al, 2016)[46]	Retrospective cohort	BLM 10 mg/kg IV	6 months	102
OBSErve Canada (Touma et al, 2017)[45]	Retrospective cohort	BLM 10 mg/kg IV	6 months	52
OBSErve Switzerland (von Kempis et al, 2019)[47]	Retrospective cohort	BLM 10 mg/kg IV	6 months	53
OBSErve pooled (Collins et al, 2020)[48]	Retrospective cohort	BLM 10 mg/kg IV	6 months	830
Mainz cohort (Schwarting et al, 2019)[46]	Prospective cohort	BLM	Up to 36 months	86
São Paulo cohort (Scheinberg et al, 2014)[42]	Prospective cohort	BLM 10 mg/kg IV	24 weeks	20
Dashiell-Aje et al, 2018[59]	Cross-sectional	BLM 200 mg SC	NA	43

Abbreviations: BLM, belimumab; IV, intravenous; OL, open label; RCT, randomised clinical trial; SC, subcutaneous.

Table 2 Impact of Belimumab on SLE Patient's HRQoL

Study	HRQoL Tool	HRQoL Data	Achievement of Improvement ≥ MCID	Achievement of Desirable Health State
Furie at al, 2008[57]	SF-36	Mean change w15–w0: no differences between pooled BLM arms and PBO	NA	NA
Wallace et al, 2009[34]	SF-36	Mean change w52–w0: PBO: 1.4 ± 0.7 BLM 1 mg/kg: 2.7 ± 0.7 BLM 4 mg/kg: 1.7 ± 0.7 BLM 10 mg/kg: 3.4 ± 0.8 (p<0.05, compared with PBO)	BLM 1 and 10 mg/kg (PCS: ≥2.5)	NA
BLISS-52 and BLISS-76 (Navarra et al, 2011, Furie et al 2011, Strand et al, 2014)[9,10,35]	EQ-5D	Mean change w52-w0: EQ-5D utility index: no differences across treatment arms. EQ-5D VAS: no differences across treatment arms	NA	Proportion of patients reporting no problems in each EQ-5D dimension: higher increase for BLM 10 mg/kg vs PBO (difference: 6.33; p<0.05) in pain/discomfort; no differences for other dimensions.
	FACIT-Fatigue	Significantly higher increase for both BLM arms compared with PBO; improvement >MCID for both BLM arms	BLM 1 and 10 mg/kg (>4)	NA
	SF-36	SF-36 PCS: significantly higher increase for both BLM arms compared with PBO (p<0.05). SF-36 MCS: significantly higher increase for BLM 1mg/kg compared with PBO (p<0.05), SF-36 subscales: significantly higher increases for both BLM arms compared with PBO in PF, BP, GH and VT	BLM 1 and 10 mg/kg (PCS/MCS: ≥2.5; subscales: ≥5)	SF-36 subscale scores lower than US population-based norms for all treatment arms
BLISS-SC (Stohl et al, 2017)[11]	FACIT-Fatigue	Adjusted mean change w52–w0: 4.4 vs 2.7 (p=0.013)	% of patients with increase ≥4 at w52: PBO 36.1%; BLM: 44.4% OR 1.4 (1.1–1.9; p=0.025)	NA
Van Vollenhoven et al, 2012[14]	FACIT-Fatigue	Mean change w52–w0: PBO: 1.8 ± 0.8 BLM 1 mg/kg: 4.7 ± 0.8 (p<0.001) BLM 10 mg/kg: 4.1 ± 0.8 (p=0.004)	NA	NA
	SF-36	PCS LS-means change w52–w0: PBO: 3.2 ± 0.6 BLM 1 mg/kg: 4.6 ± 0.6 (p=0.03) BLM 10 mg/kg: 4.8 ± 0.6 (p=0.01)	NA	NA
Doria et al, 2018[38]	FACIT-Fatigue	Mean change w52–w0: PBO: 3.6 BLM: 5.4 Difference: 2.1 (0.2–4.1; p=0.032)	% of patients with increase ≥4 at w52: PBO 33.3%; BLM: 44.8% OR 1.8 (1.1–3.0; p=0.020)	NA
Gomez et al, 2021[37]	FACIT-Fatigue	OR FACIT-Fatigue <30 for BLM 10 mg/kg vs PBO: 0.53 (0.34–0.81; p=0.004)	NA	NA
	SF-36	OR SF-36 GH <NP5 for BLM 10 mg/kg vs PBO: 0.59 (0.39–0.91; p=0.016). No significant differences for SF-36 PCS/MCS and other SF-36 subscales	NA	SRI-4 responders reported lower SF-36 subscale scores than population-based norms
Borg et al, 2021[39]	FACIT-Fatigue	OR FACIT-Fatigue <30 for BLM use vs PBO: 0.76 (0.61–0.96; p=0.034)	NA	NA
	SF-36	OR SF-36 PF <NP5 for BLM use vs PBO: 0.78 (0.63–0.97; p=0.025). No significant differences for SF-36 PCS/MCS and other SF-36 subscales	NA	NA

(*Continued*)

Table 2 (Continued).

Study	HRQoL Tool	HRQoL Data	Achievement of Improvement ≥ MCID	Achievement of Desirable Health State
Lindblom et al, 2021[36]	EQ-5D	NA	NA	Proportion of patients with EQ-5D FHS[a] at week 52: PBO: 19.4% BLM 1 mg/kg: 23.6% (p=0.029) BLM 10 mg/kg: 26.1% (p=0.001) US population-based norms: 48.7%
Maslen et al, 2021[58]	SF-36	SF-36 PCS LS-means at w52: PBO 4.2 ± 0.7 BLM: 5.4 ± 0.7 (p=0.065)	NA	NA
BEL 112233 (Strand et al, 2019)[41]	FACIT-Fatigue	Mean change from baseline: sustained increase >MCID throughout 5 years. Increase at year 6: 3.7	% of patients with increase ≥ 4 at year 6: 46.4%	NA
	SF-36	Mean change from baseline SF-36 PCS: sustained increase >MCID throughout 6 years. Increase at year 6: 4.8. SF-36 MCS: increase >MCID for the 1–5 years period. Increase at year 6: 2.7. SF-36 subscales: sustained increase >MCID for 7/8 subscales through year 6	BLM 10 mg/kg (PCS/MCS: ≥2.5; subscales: ≥5) % of patients with increase ≥MCID at year 6 SF-36 subscales: 37.5% [RE] to 52.1% [PF, GH]	NA
Swedish cohort (Parodis et al, 2017)[15]	EQ-5D	EQ-5D index score: Increase at month 12: 0.06 Increase at month 24: 0.08.	NA	NA
	VAS general health	Sustained decrease from month 3 until month 48: Month 12: 14.6 mm Month 24: 18.4 mm	NA	NA
	VAS fatigue	Sustained decrease from month 3 until month 48: Month 12: 12.0 mm Month 24: 15.2 mm	BLM 10 mg/kg (reduction >13.9)	NA
	VAS pain	Sustained decrease from month 3 until month 48: Month 12: 13.8 mm Month 24: 17.4	NA	NA
	HAQ-DI	Decrease at month 12: 0.14 Decrease at month 24: 0.18	NA	NA
Swedish cohort (Parodis et al, 2019)[16]	EQ-5D	No significant changes in mean score from baseline	NA	NA
	FACIT-Fatigue	Sustained increase >MCID from month 6 to 24. Increase at month 24: 6.5 (5.0)	BLM 10 mg/kg (>4)	NA
	HAQ-DI	Significant improvements at month 6 and 12 from baseline	NA	NA
	SF-36	SF-36 PCS: sustained increase >MCID throughout 24 months. Increase at month 24: 6.1 (7.0). SF-36 MCS: increase >MCID at month 12; no significant increases at other time points	BLM 10 mg/kg (PCS/MCS: ≥2.5; subscales: ≥5)	SF-36 subscale scores lower than Swedish population-based norms for all treatment arms
Italian cohort (Gatto et al, 2020)[22]	VAS fatigue (0–10)	Mean VAS fatigue score: Baseline: 5.2 ± 3.0 Month 12: 3.3 ± 2.6 Month 24: 2.8 ± 2.7 Month 36: 2.3 ± 2.7 Month 48: 2.4 ± 3.0 (p<0.001)	NA	NA

(*Continued*)

Table 2 (Continued).

Study	HRQoL Tool	HRQoL Data	Achievement of Improvement ≥ MCID	Achievement of Desirable Health State
OBSErve Germany (Schwarting et al, 2016)[46]	Physician-assessed fatigue	Proportion of patients who improved: >50%: 25%. 20–50%: 57.5% <20%: 17.5%	NA	NA
OBSErve Canada (Touma et al, 2017)[45]	Physician-assessed fatigue	Proportion of patients who improved: >50%: 26.7% 20–50%: 53.3% <20%: 20%	NA	NA
OBSErve Switzerland (von Kempis et al, 2019)[47]	Physician-assessed fatigue	Proportion of patients who improved: ≥50%: 15.8% 20–49%: 42.1% <20%: 42.1%	NA	NA
OBSErve pooled (Collins et al, 2020)[48]	Physician-assessed fatigue	Proportion of patients who improved: ≥50%: 42% 20–49%: 26% <20%: 23%	NA	NA
Mainz cohort (Schwarting et al, 2019)[44]	FSMC	Significant improvement from baseline in Fatigue score total, motoric and cognitive	NA	NA
São Paulo cohort (Scheinberg et al, 2014)[42]	FACIT-Fatigue	Mean FACIT-Fatigue score Baseline: 37.6 ± 3.8 Month 6: 48.8 ± 3.3	NA	NA
Dashiell-Aje et al, 2018[59]	Fatigue Likert scale	Change after treatment: More severe: 5% No change: 19% Somewhat less severe: 50% Much less severe: 26%	NA	NA

Note: [a]EQ-5D-FHS: full-health state (EQ-5D index score = 1).
Abbreviations: BP, Bodily Pain; CI, Confidence Interval; EQ-5D, EuroQol 5-Dimension health questionnaire; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FSMC, Fatigue Scale for Motor and Cognitive functions; GH, General Health; HAQ-DI, Stanford Health Assessment Questionnaire Disability Index; HRQoL, Health-Related Quality of Life; LS-means, least-squared means; MCID, Minimal Clinically Important Difference; MCS, Mental Component Summary; MH, Mental Health; OL, open label; PCS, Physical Component Summary; PF, Physical Functioning; OR, Odds Ratio; RE, Role Emotional; SF, Social Functioning; SF-36, Short Form 36; VT, Vitality.

Pivotal Phase III RCTs of Belimumab: BLISS-52 and BLISS-76

In the two pivotal phase III RCTs of belimumab, patients with SLE received IV infusions of belimumab at a dose 1 mg/kg or 10 mg/kg, or placebo. The BLISS-52 and BLISS-76 trials had similar design but differed in the length of follow-up (52-week follow-up in BLISS-52 and 76-week follow-up in BLISS-76). Both trials met the primary efficacy endpoint, ie, attainment of SLE Responder Index 4 (SRI-4) at week 52, as well as key secondary endpoints such as lower frequencies of severe flares and reductions in glucocorticoid doses n belimumab-treated patients versus placebo-receivers.[9,10]

A post-hoc analysis these trials investigated HRQoL outcomes in belimumab-treated patients compared with placebo-receivers,[35] and reported greater improvements in SF-36 PCS at week 52 in both belimumab arms compared with patients who received placebo, and greater improvements in SF-36 MCS in patients who received IV belimumab 1 mg/kg compared with placebo-receivers. Regarding SF-36 subscales, belimumab induced greater improvements in PF, BP, and GH. However, despite the documented improvements, HRQoL at week 52 was poorer than that of age- and sex-matched US population-based norms. Mean changes in EQ-5D utility index scores or VAS scores did not differ across treatment arms. Lastly, improvements in FACIT-F and SF-36 VT scores were greater in both belimumab arms compared with patients who received placebo and exceeded minimal clinically important differences (MCIDs).

In subsequent post-hoc analyses, the proportion of patients who reported EQ-5D full health state at week 52 was greater in belimumab-treated patients compared with placebo-receivers, as well as in SRI-4 responders compared with

non-responders.[36] Moreover, greater proportions of patients in the belimumab 10 mg/kg arm versus placebo reported "no problems" at week 52 regarding mobility (odds ratio, OR: 1.32; 95% confidence interval, CI: 1.00–1.74; P = 0.049), self-care (OR: 1.46; 95% CI: 1.02–2.10; P = 0.038), and pain/discomfort (OR: 1.51; 95% CI: 1.14–1.99; P = 0.004).

Another post-hoc analysis that focused on the SLE patients who attained the primary efficacy endpoint of the trials (SRI-4) showed that use of IV belimumab 10 mg/kg was independently associated with a lower probability of adverse self-reported SF-36 PF (OR: 0.59; 95% CI: 0.39–0.91; P = 0.016) and FACIT-F scores <30 (OR: 0.53; 95% CI: 0.34–0.81; P = 0.004) at week 52.[37] It is however worth nothing that self-reported scores were worse than those derived from age- and sex-matched norms in all SF-36 subscales. Adverse SF-36 outcome was defined in line with research in rheumatoid arthritis[38] as scores ≤ the normative 5th percentile in an age- and sex-matched US population-based sample, while adverse FACIT-F outcome was defined as scores <30.[32] The benefit from belimumab use regarding prevention of both adverse physical HRQoL outcome and severe fatigue was later corroborated in a post-hoc analysis that included the entire study population from the BLISS-52 and BLISS-76 trials.[39] Lastly, analyses in the subgroup of patients with positive anti-dsDNA levels and/or low complement levels at baseline reported greater improvements in HRQoL and fatigue in belimumab-treated patients compared with placebo-receivers.[14,40]

Open-Label Extension Phases

A subset of patients who completed the BLISS-76 trial continued in an open-label extension study, in which they continued to receive belimumab (belimumab/belimumab arm; n = 177), or switched to belimumab (placebo/belimumab arm; n = 91). These patients were followed for up to 6 years. In this study, patients reported sustained improvements in SF-36 PCS (mean change ± standard deviation, SD from baseline through year 6: 3.4 ± 8.6) and MCS (mean change ± SD from baseline through year 6: 2.5 ± 10.1), which were greater than MCIDs.[41] Percentages of patients reporting increases in SF-36 subscale scores ≥MCID at the end of follow-up (year 6) were overall greater for the physical subscales of SF-36; they ranged from 37.5% (RE) to 52.1% (PF, BP, and GH). Despite improvements deemed clinically important, SF-36 scores were, again, considerably lower compared with reference normative values derived from the US general population. Moreover, patients reported sustained improvements in FACIT-F scores (mean change ± SD from baseline through year 6: 3.7 ± 11.8), which exceeded the MCID in comparisons over the first five years, but not at further assessments (year 6).

Subsequent RCTs

The BLISS-SC trial evaluated the efficacy and safety of weekly SC injections of belimumab 200 mg in patients with SLE.[11] Patients who received belimumab self-reported improvements in FACIT-F scores at week 52 which were deemed clinically important and were statistically greater than those reported by placebo-receivers (mean increase: 4.4 versus 2.7; P = 0.01). Moreover, the percentage of patients who improved in FACIT-F at an extent that exceeded the MCID was greater among belimumab-treated patients than among placebo-receivers (44.4% versus 36.1%; P = 0.02). Three additional phase III RCTs of belimumab have been conducted, BLISS-Northeast Asia[42] and EMBRACE[43] for active SLE, yet excluding severe active renal SLE, and BLISS-LN[13] for active LN, but no results on HRQoL have been reported from these trials.

Observational Studies

Efficacy and safety of belimumab have also been reported from several cohorts around the world. In a cohort of 20 patients from Brazil, improvements in FACIT-F scores from baseline (37.6 ± 3.8) through month 6 (48.8 ± 3.3) were documented.[44] In a cohort of 58 patients from three tertiary referral centres in Sweden, SLE patients reported a sustained increase in EQ-5D index score over 24 months on treatment with belimumab, as well as decreases in 100-mm VAS pain (mean change from baseline to month 24: 17.3 mm; P < 0.001), VAS fatigue (mean change from baseline to month 24: 15.1 mm; P = 0.007), VAS general health (mean change from baseline to month 24: 18.4 mm; P < 0.001), and Stanford Health Assessment Questionnaire Disability Index (HAQ-DI; mean change from baseline to month 24: 0.18; P = 0.014).[15] In a subsequent study of belimumab-treated patients from the Karolinska University Hospital in Stockholm, SLE patients reported early and continuous, gradual improvements in SF-36 PCS over time on belimumab therapy, which exceeded the MCID at the

assessments of month 12 and 24; self-reports concerning SF-36 MCS yielded less consistent results, which improvements documented at month 12 only.[45] Importantly, patients self-reported considerable HRQoL impairments over time within all SF-36 domains compared with an age- and sex-matched normative reference group, despite the documented improvements. Regarding fatigue, patients in that study self-reported sustained improvements that exceeded the MCID in FACIT-F scores, as well as in SF-36 VT subscale scores.[45]

In a study from Mainz in Germany, levels of antibodies against the NR2 subunit of the N-methyl-D-aspartate receptor (anti-NR2) were found to correlate with fatigue and were higher in patients with severe fatigue compared with SLE patients with moderate, mild, or no fatigue.[46] In a subgroup of 68 belimumab-treated SLE patients who received treatment for at least 6 months, improvements in fatigue were documented and included improvements within subscales for motor and cognitive functions; those were accompanied by decreases in serum levels of anti-NR2 antibodies.[46] In a study from Italy that comprised 466 belimumab-treated patients with SLE, sustained decreases in VAS fatigue scores were documented throughout a follow-up of up to 48 months, yielding a change from 5.2 ± 3.0 at baseline to 2.4 ± 3.0 at month 48 ($P < 0.001$).[19]

The observational programme "evaluation Of use of Belimumab in clinical practice Settings" (OBSErve) comprised a series of studies carried out in 6 different countries (Argentina, Canada, Germany, Spain, Switzerland, USA).[47–49] In these studies, physician-assessed changes in fatigue at month 6 compared with baseline were reported. In the pooled OBSErve study population that comprised 372 patients with SLE, 23% of the patients experienced minimal or no improvement in fatigue (<20% improvement), whereas 44% experienced a ≥50% improvement.[23]

Discussion

We reviewed the literature in a systematic manner to gain insight in the impact of belimumab on HRQoL. Results from six studies suggest that belimumab induces clinically meaningful improvements in several aspects of HRQoL and fatigue; these results mainly are based on assessments using the SF-36 and FACIT-F scales. Importantly, the benefit from belimumab was greater within physical compared with mental aspects of HRQoL.[41]

Several studies have shown that belimumab exerts clinically important and sustained improvements on physical aspects of HRQoL. Two RCTs of belimumab demonstrated improvements induced by belimumab in the physical components of SF-36 that exceeded thresholds set to define minimal clinically important differences, and were greater than improvements seen in the placebo arm; importantly, these improvements were sustained in the open-label extension phases of these RCTs.[35,41] Along the same lines, benefits from belimumab exceeded the MCID regarding SF-36 PCS, yet not SF-36 MCS, in a Swedish real-life clinical setting.[45]

Moreover, the positive effects of belimumab on fatigue have been consistently demonstrated in RCTs and cohort studies. In the RCTs of IV belimumab, use of both low-dose and high-dose belimumab was associated with clinically important improvements in fatigue, along with lower proportions of belimumab-treated patients reporting severe fatigue compared with placebo receivers.[9,10,35,37,39] Similarly, in the RCT of SC belimumab, higher proportions of patients treated with belimumab experienced clinically important improvements in fatigue compared with patients who received placebo.[11,40] Several cohorts of SLE patients exposed to belimumab therapy from South America, North America, and Europe have used various instruments to assess fatigue, eg, FACIT-F, Fatigue Scale for Motor and Cognitive functions (FSMC), patient-reported visual analogue scales, and physician-based reports [11,15,19,23,44–49] Despite the diversity across study populations and outcome measures, a consistent benefit from belimumab was noted regarding fatigue.

However, despite the documented improvements, results from the phase III RCTs of belimumab,[35] their open-label extension phases,[41] as well as real-life studies,[45] consistently showed considerable HRQoL impairments in patients with SLE compared with age- and sex-matched population-based reference data, even after documented improvements in HRQoL over time on treatment, particularly within physical aspects of HRQoL. As shown in a study from our group, considerable impairments were also shown in the subgroup of SLE patients who had attained adequate response to therapy based on clinical and laboratory parameters; importantly, this was shown to be partially driven by a negative impact of established irreversible end-organ damage.[37]

In a post-hoc analysis of the BLISS-52 and BLISS-76 trials of belimumab from our group, approximately one-fourth of the SLE patients self-reported EQ-5D full health state (FHS) after a 52-week-long therapeutic intervention; FHS corresponds to the best possible health experience.[36] Interestingly, EQ-5D FHS showed ability to distinguish SRI-4 responders from non-responders, as well as belimumab-treated patients from placebo receivers,[36] lending support to the usefulness of EQ-5D FHS as a patient-reported outcome fitting the treat-to-target concept in SLE,[50] and warranting analysis of its association with long-term outcomes, eg, organ damage accrual.

It is worth noting that the evidence on the impact of belimumab on HRQoL compiled in the present review derive solely from generic patient-reported outcome measures. The use of generic instruments for HRQoL assessment has advantages, such as allowing comparisons with other disease populations as well as with the general population. However, their main limitation is that generic instruments may not capture aspects of particular relevance for SLE patient populations. Disease-specific tools, eg, the LupusQoL[51] and LupusPro,[52] allow researchers and health-care providers to investigate such aspects that may be omitted in generic tools, including body image, intimate relationships, and sleep. Furthermore, disease-specific tools have been shown to be more responsive to changes compared with generic tools in certain contexts.[53,54] We herein advocate the combination of generic and disease-specific HRQoL instruments in clinical trials and cohort studies, aiming to obtain a comprehensive understanding of the SLE patients' HRQoL experience.[5]

Belimumab may exert its benefits in multiple ways, eg, through overall disease control and corticosteroid-sparing effects,[55,56] or through favourable effects on symptoms such as fatigue, that constitutes a major patient complaint, the latter being shown to be the case irrespective of the impact of belimumab on physician-assessed disease activity.[37,46] In this regard, the documentation of correlations between fatigue and levels of anti-NR2 antibodies was of particular interest, along with the observed reductions both in the degree of fatigue and anti-NR2 antibody levels upon belimumab therapy;[46] together, these observations suggest that belimumab may exert favourable effects that specifically concern fatigue, along with the overall clinical benefit and benefit in HRQoL.

Concluding Remarks

Along with the well-documented clinical efficacy of belimumab in patients with SLE and an overall satisfactory safety profile, there is robust evidence that belimumab induces clinically meaningful improvements in HRQoL, especially within physical aspects of HRQoL and in fatigue. Despite improvements in clinical and immunological features upon therapy, HRQoL perception remains unsatisfactory for a substantial percentage of SLE patients. In this regard, individualised and multicomponent management comprising non-pharmacological interventions along with optimised pharmacotherapy should be considered towards better outcomes in this highly heterogeneous patient population. Finally, our review made apparent an urgent need for optimisation of the use of patient-reported outcome measures, eg, through consistent use of MCIDs and comprehensive reports of not only changes in perceptions but also attainment of desirable states. Such optimisation is desirable both in research and clinical practice.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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