The use of combination monoclonal antibody therapies in lupus – where are we now?

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Introduction

Unlike the successful development and regulatory approval of various monoclonal antibody therapies patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients, [1] few biologic therapies are approved for use in systemic lupus erythematosus [SLE]. In 2011 belimumab the anti-BAFF monoclonal, was approved by the Federal Drug Administration [FDA] for non-renal SLE, and in 2020 lupus nephritis [LN]. Anifrolumab, which blocks the type 1 interferon receptor was approved by the FDA in 2021 and, although not approved by the FDA; the B-cell depleting, the anti-CD20 agent Rituximab [RTX] [and its biosimilars] are recommended for refractory LN by the American College of Rheumatology [2] and its European equivalent [3]. Given the heterogeneity of SLE, combinations of monoclonal antibody therapies may be effective treatment for some patients. There have now been three reports [4, 5, 6] describing the use of combination therapy with rituximab and belimumab in LN and non-renal lupus. The primary endpoint was met in BEAT-LUPUS (reduction in anti-dsDNA antibodies) but not in BLISS-BELIEVE (using SLEDAI-2K). The CALIBRATE trial was a safety study. Reviewing these trials in detail, important differences emerge.

i) Design issues

The phase 2 CALIBRATE trial assessed safety and mechanism of action but was not designed to demonstrate therapeutic benefit. Phase 2b BEAT-LUPUS and phase 3 BLISS-BELIEVE trials evaluated efficacy but for different durations. BLISS BELIEVE patients evaluated for longer (52W Treatment period + 52W observational), compared to BEAT-LUPUS which terminated after 52 weeks.

ii) Study population

CALIBRATE had 43 patients, BEAT-LUPUS 52 and BLISS-BELIEVE 292.

No bias regarding the gender and age of patients in these trials was evident but CALIBRATE had more Black patients than the others [see table 1].

BLISS-BELIEVE only enrolled non-renal patients, excluding those with LN and central nervous system lupus. In BEAT-LUPUS almost 40% in both arms had renal disease and in CALIBRATE all had recurrent or refractory LN. BEAT-LUPUS had a total of 20 LN patients (10 in each arm) but only two had had a kidney biopsy within three months of the trial commencing – one each with class V and class III/IV – compared to almost 40% patients with class IV & V in CALIBRATE. Severity of kidney disease can lead to important differences in outcome and limits comparison of results between these trials.

To assess disease activity, all three trials used anti-dsDNA antibody levels. BLISS-BELIEVE had fewer patients (60%) with high anti-dsDNA antibody levels (in BEAT LUPUS and CALIBRATE it was 90%). BEAT-LUPUS and CALIBRATE used the BILAG score and SLEDAI-2K, respectively. Using different activity criteria, makes it difficult to compare the level of baseline disease activity.

In CALIBRATE all patients had previously been treated with cyclophosphamide [CYC] or mycophenolate mofetil [MMF] and treatment in the prior 12 months with RTX or another anti B cell agent was forbidden.

In BEAT-LUPUS 14 patients had previous RTX treatment, seven within two years. At screening of the patients given RTX + Belimumab 92% received immunosuppressants (IS) drugs compared to 73% in the RTX only group (see Table 1 for details) raising the question whether this could have influenced the outcome. Comparative data for BLISS-BELIEVE have not been confirmed.

iii) Arms and medications allowed during the study

In CALIBRATE, each patient had IV methylprednisolone 100mg + RTX 1000mg + CYC 750mg IV at W0 and W2. They were randomized 1:1 at W4 in two different arms: RC (RTX + CYC) (22 patients) with no additional treatment and RCB (RTX + CYC + Belimumab) (21 patients) receiving Belimumab IV 10mg/kg W4, W6, W8 and then every 4W through W48. During the study, hydroxychloroquine [HCQ] was allowed and 72% patients were receiving angiotensin-converting enzyme inhibitors [ACE] or angiotensin II receptor blockers [ARB]; 54% of patients received both. Other IS or additional RTX were forbidden (unless patients met discontinuation criteria).

In BEAT-LUPUS, all patients received RTX during the 4 to 8W after 1st screening (two 1g doses administered 2W apart) and then randomized to receive placebo (PBO) or IV Belimumab 10mg/kg W0, W2, W4 and then every 4W through 52W. During the trial only 15mg/w of MTX; 1g/day of MMF, 1mg/kg AZA (Azathioprine), after randomization were allowed. No dose changes of antimalarial drugs after 1st screening were allowed.

BLISS-BELIEVE had three different arms. The Belimumab/PBO arm (n=72) had SC Belimumab 200mg/w for 52W + PBO IV W4 and W6, the Belimumab/RTX (n=144) had SC BEL 200mg/w for 52W + RTX 1000mg IV W4 and W6 were both followed by a 52W observational phase; and Belimumab/Standard therapy (n=76) had SC Belimumab 200mg/w + ST for 104w (including IS).

Thus, although each trial used Belimumab and RTX, CALIBRATE also used CYC at W0 and W2, which could be beneficial and explain the different patient responses. BLISS-BELIEVE used RTX after Belimumab while BEAT-LUPUS used RTX followed by Belimumab, which begs the question whether the depletion of B cells before Belimumab can deliver longer benefit.

iv) Endpoints and Outcomes

Endpoints of the three trials were intrinsically different. The primary endpoint in CALIBRATE was safety and it was achieved [no statistically significant differences between the arms]. BEAT-LUPUS and BLISS-BELIEVE had disease activity as the primary endpoint but with different perspectives – BLISS-BELIEVE used a clinical end point (Proportion of patients with a state of disease control at 52W -SLEDAI-2K </= 2 without IS + PDN </= 5mg/day) with the proportion of patients in a state of disease control at 52W, while BEAT-LUPUS used a serologic end point. BLISS-BELIEVE did not achieve its primary endpoint but showed a longer duration of disease control at W52, indicating that long term use of this combination may be therapeutically advantageous, by keeping the BAFF levels lower for longer.

Conclusion

Belimumab with RTX appears to be safe with no increase in the incidence of adverse events encouraging further studies to confirm the hypothesis that a surge in BAFF levels after RTX can trigger SLE exacerbations and that belimumab after RTX can bring the disease under better control. Although more information is needed about the BLISS-BELIEVE Trial, there are encouraging signs that combining RTX with Belimumab might be of use in some, but clearly, not all patients.

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Trial	CALIBRATE	BEAT-LUPUS	BLISS-BELIEVE
Phase	Phase 2	Phase 2b	Phase 3

Designed to	Assess safety and mechanism of action Generate preliminary efficacy data	Obtain preliminary evidence of effectiveness and safety. Intention-to-treat	Intention to treat. Evaluate efficacy, safety and tolerability
Duration	96W (48W treatment period + 48W observational phase)	52W	104W (52W Treatment period + 52W observational)
N° of patients/n° of patients in each arm	43 (22 patients in RC arm vs 21 patients in RCB arm)	52 (26 patients in RTX/PBO arm vs 26 patients in RTX/BEL arm)	292(72 patients in BEL/PBO arm vs 144 patients in BEL/RTX 144 arm vs 76 patients in BEL/ST)
Gender/age/ethnicity	Female 81.8% vs 90.5%* Mean age 32.3 vs 34.5 years White 31.8 vs 42.9% * Non-white: black 40.9 vs 42.9%; Asian 13.6 vs 9.5%; *other 13.6 vs 4.8%* Hispanic or Latino 45.5 vs 23.8%*	Female 88% vs 81% * Mean age: 41 vs 38 years White: 65 vs 50%* Non-white: black 12 vs 12%; South Asian 8 vs 15%; Chinese 4 vs 8%; other 11 vs 15%*	Female 91.7% vs 89.6% vs 96.1%* Mean age 40.5 years White - Arabic/North African Heritage 0 vs 0.7 vs 0.7%* White – White/Caucasian/European Heritage 54.2 vs 69.4 vs 61.8%* Asian – Central/South Asian Heritage 0 vs 0.7 vs 1.3%* Asian – East Asian Heritage 9.7 vs 9.7 vs 13.2%* Asian – South East Asian Heritage 4.2 vs 1.4 vs 1.3%* African American/African Heritage 29.2 vs 15.3 vs 17.1%* American Indian or Alaskan Native 1.4 vs 2.1 vs 3.9% * Native Hawaiian or other Pacific Islander 1.4 vs 0.7 vs 0%*
Type of patients	Recurrent or refractory lupus nephritis previously treated with CYC or MMF. Positive ANA+ and/or anti-dsDNA positive at screening	Classification criteria for SLE Positive anti-dsDNA at least once in previous 5Y and were due to be treated with RTX (failure of conventional therapy)	Active SLE (according ACR) Excluded patients with LN and SNC lupus
Disease duration?	84% of patients had LN for > than 1year. Mean (years) 4.8 years in RC vs 6.8 RCB (all patients = 5.8 years)	Mean (years) 9.2 vs 11.8; Median 6.6 vs 10.3	No data available
Type of disease activity assessment at BL	Anti-dsDNA >/=30 90.9% vs 90.5%*	Anti-dsDNA >/=20 88 vs 92% * Active renal disease at 1st screening (BILAG A or B renal score) Majority of patients with IS, active disease (>/= 1 BILAG B) >/= 1A: 31 vs 23%* >/= 1A or 2B: 35 vs 50%* >/= 1A, 2B or 1B: 77 vs 88%* Base line mean serum IgG anti-dsDNA was higher in RTX/BEL	Anti-dsDNA positive (>/=30) at Baseline: 61.1% vs 66% vs 57.9%* *SLEDAI-2K >/= 6 at screening (Randomization with >/= 9 vs >/=10) - Mean SLEDAI score 10.3
B cell at BL	B cell baseline were similar between arms (CD19 count 105.5 vs 143)*	CD19 count 7-10 days before randomization (CD19 count <0.01x10^9: 22 patients (85%) in both groups)*	No data available
Hypogammaglobulinemia	2 (9.1%) vs 4 (19%)*	No data available	No data available
Low C3 Low C4	18 (81.8%) vs 16 (76.2%)* 10 (45.5%) vs 8 (38.1%) *	13 (50%) vs 11 (42%)* No data available	No data available No data available
- renal pts	ALL recurrent ou refractory LN All UPCR>1 (24H CU) + kidney biopsy within the prior 18 months documenting ISN/RPS Class III or IV alone, or in combination with Class V. If the biopsy was >3 months prior to screening, active urine sediment, UPCR>3, or increasing UPCR over the prior 3 months was required Baseline median UPCR 3.1 (more pts with UPCR >3 in RC arm (14 vs 8)* but mean UPCR, eGFR, albumin similar) Lupus Nephritis classification: Class III 1 (4.5%) vs 1 (4.8%)* Class IV 8 (36.4%) vs 7 (33.3%)* III + IV 3 (13.6%) vs 5 (23.8%)* IV + V 10 (45.5%) vs 9 (38.1%)*	10 vs 10 * 2 patients had renal biopsy within <3M before the study commencing 1 patient - class V 1 patient – class III/IV	0
- non-renal pts	0	16 vs 16*	292*
Previous Therapy	Previously treated with CYC or MMF. Prior treatment at any time RTX or another anti B cell in the prior 12M -> not allowed	Previous RTX: 8 vs 6*; previous RTX within 2 years: 3 vs 4* At screening and randomization, the majority were receiving IS: MMF 58 vs 73%*; AZA 8 vs 8%*, MTX 8 vs 11%* PDN 92 vs 85%* (median PDN dose 14 vs 10mg/d); concomitant IS 73 vs 92%* concomitant IS or PDN 100% vs 92%*	No data available but patients were randomized according to: Iimmunosuppressant (yes or no) Steroids – PDN </=10mg vs >10mg/day) Exclusion criteria included having until: 364 days before: BEL, RTX, ABA, or 3 or more courses of systemic steroids 90 days before: anti-TNF, IL1, IV IG, high doses PDN or Plex 60 days before: non biological agents, IV CYC, steroid injection
Arms	**All:** IV MP 100mg + RTX 1000mg + CYC 750mg IV W0 and W2 + PDN 40 mg/day was initiated with a forced taper to 10 mg/day by W12, followed by <10mg/day through W96	**1:1** **RTX** during the 4 to 8W after 1st screen Dose fixed: two 1g doses administered 2W apart **+ PBO** (26) **RTX**	**1:2:1** **A - BEL/PBO** (72): SC BEL 200mg/w for 52W + PBO IV W4 and W6 -> 52W observational phase (no treatment)

	Randomized at W4 **1:1** **RC** (22): no additional treatment **RCB** (21): BEL IV 10mg/kg W4, W6, W8 and then every 4W through W48 (2g RTX + 13 doses of SC BEL; 1ª dose 2W after RTX) Allowed throughout the study - HCQ (72% of patients) - ACE or ARB (72% of patients) and both (54% of patients) Other IS or extra RTX not allowed (unless patient with discontinuation criteria)	**+ IV BEL** 10mg/kg W0, W2, W4 and then every 4W through 52W (26) Mean time between screening and randomization 41.8 vs 44.7days, median time 41.5 vs 42.5 days. Admitted up to mg of 20PDN/day from randomization (encouraged to tapper to half of initial dose in 6M) Only 15mg/w MTX; 1g/day of MMF, 1mg/kg AZA, after randomization No dose changes of antimalarial drugs after 1st screening	**B- BEL/RTX** (144): SC BEL 200mg/w for 52W + RTX 1000mg IV W4 and W6 -> 52W observational phase (no treatment) (2g RTX + 52 doses of iv BEL) **C - BEL/ST** (76): SC BEL 200mg/w + ST for 104w (including IS) A and B – premedication (MPDN IV 100mg + oral AH + acetaminophen) Observational phase only antimalarials, non-steroids anti-inflammatory and steroids (</=) 5mg/day) were allowed A and B: discontinue IS at or prior W4 A, B, C: After W12 steroids forced taper -> target PDN </= 5mg/day by W26 (Treatment failure if not possible) C – continues treatment if under stable IS Anti-TNF, biologics with effects on the immune system, IV Immunoglobulin, IV CYC and PlEx – not allowed
1º end-points - What was it?	Safety: Proportion of patients with at least one grade 3 or higher infectious AE at or prior W48	Anti-dsDNA IgG W52	Proportion of patients with a state of <u>disease control</u> at 52W -SLEDAI-2K </= 2 without IS + PDN </= 5mg/day at W52 (BEL/PBO vs BEL/ST)
- Was it achieved?	23% vs 9.5%* Not statistically significant. ALL infectious AEs resolved. ALL patients had at least 1 AE. No deaths and no opportunistic infections.	Lower on RTX/BEL and 70% greater reduction (24W) (p<0.001); Patients in RTX/BEL arm achieved a 71% greater reduction in IgG anti-dsDNA relative to baseline; At 52W levels were lower in RTX/BEL.	16.7% vs 19.4% vs 25.5%* - Not statistically significant
2º end-points - What was it	Proportion of patients with B cell reconstitution (baseline B cell count) and proportion of patients with grade 4 hypogammaglobulinemia (IgG<300mg/dL + grade 3 or greater infectious AEs)	Time from randomization to the 1st moderate disease flare (>/= 2 BILAG2004 B flares but no A flares) or severe disease flare (>/=1BILAG2004 A flare) (flares requires worsening or new manifestations of lupus)	Proportion of patients in <u>clinical remission</u> at W64 (SLEDAI-2K =0, without IS or ST) and <u>disease control</u> at W104
- Was it achieved?	B cell depletion was achieved in both groups at W12, but B cells remained consistently lower in RCB arm (W60 – 12W after BEL was discontinued – Geom mean : 53 vs 11*) <u>B cell reconstitution</u> W24 5 vs 0*, *p=0.041*; in the RC group - the mean number of B-cells was higher in NR (vs CR and PR in the RC) W48 2 of 8 patients in RC vs 0 of 12 in RCB arm <u>Mean IgG levels</u> Lower in RCB (but above considered hypogammaglobulinemia): 1410 mg/dL vs 904.5mg/dL *(p=0.022)* No patients with grade 4 hypogammaglobulinemia; just 1 patient in RC arm with IgG <300mg/dL, not infectious complications <u>% naïve B</u> cells was < RCB, compare to BL and to RC, with concomitant increases in the % of transitional Bcells and class-switched IgD -memory cells. Differences were significant W24, W48, W60 (p<0.01) <u>Autoreactive ANA+ B cells</u> W48 -predominant subpopulation were transitional cells in both. But in RCB: <% pf ANA+ naïve cells (*p=0.0176*); higher % of class-switched IgD-memory (*p=0.0082*) and CD27IgD double negative cells (*p=0.0026*) % of ANA+naïve cells was increased in 5 of 7 patients in RC arm and decreased in 8 of 9 patients in RCB (*p=0.0349*) - Relative % of ANA+ transitional cell > from BL in all pts → *BEL delays reconstitution of ANA+naïve cells by inhibiting maturation of ANA+ transitional B cells.* - Higher % ANA+ anergic cell within peripheral blood B cells in RCB – not statistically significant	<u>Key secondary outcomes</u> - Cumulative steroid dose - Proportion of patients with PDN 7.5mg/d or less at W48 and at W52 - Proportion of patients successfully reducing ST dose by 50% (if randomization dose was >/= 10mg/d) or reaching a dose of 5mg/d or less (if randomization dose was <10mg/d) , without having a flare → ALL the above were similar in both groups Safety: proportion of patients with AEs and serious AEs at W52 -> similar in both groups People who withdrew (similar BEL vs PBO) Fewer flares in RTX/BEL 7 vs 10* (p<0.03) BEL reduce the risk of a severe flare over 52W 10 severe flares in PBO arm vs 3 severe flares in BEL arm *(p=0.033)* Differences in treatment effect on the combined outcome of moderate and severe flares did not achieve statistical significance	W64: 5.6% vs 6.3% vs 10.6%* W104: 6.9% vs 11.1% vs 21.3* Not statistically significant
Other endpoints	Prospectively efficacy endpoints (14 pts at W96) Complete response: 1) UPCR <0.5 (24H Urine Collection) 2) eGRF >/= 120ml/min/1.73 or if <120ml/min/1.73 then >80% of eGFR at entry 3) adherence to the PDN dosing provisions Partial response: Same as CR but UPCR only >50% improvement from baseline. Patients with overall response (PR+CR) at W24, highest value at W48 9/22 (41%) vs 11/21 (52%) (p=0.452)*; W96 -> similar at all time points Most pts who failed treatment did so due <u>to LN</u> ; higher nº of patients who were withdrawn prior to week 48 in the RC due to lack of renal response or related to LN	No deaths Incidence of infections of any grade, serious or total AEs, withdrawals due to AEs – no difference Suicidal intention – 2 vs 0 * Depression like symptoms – similar Serum IgG remained within the normal range in the majority of pts. IgM and IgA slightly lower in BEL. C3 no differences at W52 B cells similar at W24 but higher in PBO at 52W p=0.031*(Faster repopulation in PBO arm?)*	Patient-reported outcomes measures: PtGA, LupusQoL, FACIT-Fatigue Score Safety endpoints (AEs – serious and of special interest) W52 Disease control duration 60.1 vs 105.4 vs 86.9*, LLDAS 27.8% vs 34% vs 29.8%*

	W48: 10/22 vs 5/21* removed due to renal flare, worsening nephritis or failure to show improvement in LN W96: C3 hypocomplementemia (61% vs 28%, p=0.049)* Non-renal flares – infrequent, no differences Among the UCPR >3 group of patients: At W48: CR + PR was 43% (6/14) vs 88% (7/8)* - *belimumab may be exerting a beneficial effect among participants with more severe LN?* Dialysis and ESRD within 2Y: 3 (14%) vs 1(5%)*		
Others Study assessments	Anti-dsDNA, hypocomplementemia and frequency of non-renal flares (BILAG)		anti-dsDNA: *Those with anti-dsDNA positive at baseline had significantly greater decrease from BL in BEL/RTX)*; ANA, C3/C4, Ig, Urine testing, hematology and blood chemistry, pregnancy test
Notes	Statistical analyses were performed in the modified intent-to-treat sample Discontinuation criteria: <25% improvement in UPCR at 24W, renal flare, AEs and investigator decision 48W after treatment with RTX: only 1/3 of patients in each group achieved CR Patients who received BEL had a lower number of B cells at all time points. Median IgG levels remain normal in both groups	10 days before randomization – patients who had require iv ATBs for infections developing after RTX and those with low IgG <4g/dL or neutropenia <1000cel/field were excluded. More patients with renal involvement achieved a complete renal response (and had no new renal flare through 52W in RTX/BEL) – but it is a small number	Treatment failures: patients in BEL/PBO or BEL/RTX who fail to respond; not meet steroids taper rules at W4 or require additional therapy Discontinued BEL study treatment at W52 for AEs: 19.4% vs18.8% vs19.7%* W52: Same AE's incidence, causing more treatment discontinuation and more serious events (infections/infestations) in BEL/RTX. AEs of special interest had no imbalance between BEL/PBO and BEL/RTX.
Conclusions	Addition to Belimumab did not increase the incidence of adverse effects	Clinical benefit of BEL after RTX, consistent with the hypothesis that a surge in BAFF levels after RTX can trigger SLE exacerbations.	Adding a single cycle of RTX to BEL did not improve disease control/remission.

Table 1 – Comparative data between trials

ACR – American College of Rheumatology ; AE – Adverse event; AZA – Azathioprine; BEL/PBO – Belimumab + Placebo arm; BEL/RTX – Belimumab + Rituximab arm; BEL/ST – Belimumab + Standard Therapy arm; CNS – Central Nervous System; CR – Complete response; CYC – Cyclophosphamide; HCQ – Hydroxychloroquine; eGFR – Estimated glomerular filtration rate; ESRD – End stage renal disease; IS – Immunosuppressants; ISN/RPS – International Society of Nephrology/ Renal Pathology Society; IV – intravenous; LN – Lupus Nephritis; MMF – Mycophenolate Mofetil; MPDN – Methylprednisolone; NR – Non responders; PBO – Placebo; PDN – Prednisolone; PR – Partial response; UPCR – Urine protein/creatinine ratio; RC – Rituximab + Cyclophosphamide arm; RCB – Rituximab + Cyclophosphamide + Belimumab arm; RTX – Rituximab; RTX/PBO – Rituximab + Placebo arm; RTX/BEL – Rituximab + Belimumab arm; SC – Subcutaneous; SLE – Systemic Lupus Erythematosus ; ST – Standard Therapy

Absolute numbers = number of patients | % = percentage of patients
*When comparing arms, they follow the order of arms description in *"Nº of patients/number of patients in each arm"*