UCL
Comprehensive Clinical Trials Unit

BEAT *Lupus*

Protocol synopsis

Introduction: The BEAT Lupus Trial is a multicentre, UK phase II, randomised, double blind, placebo-controlled CTIMP investigating the safety and efficacy of Belimumab after B cell depletion therapy (which has been given as standard of care) in patients with active Systemic Lupus Erythematosus resistant to conventional therapy in accordance with NHS England guidelines.

Aim: We and other investigators have pioneered using Rituximab (B cell depletion therapy) for patients with SLE but randomised controlled trials have failed to prove efficacy. Our most recent biomarker data (Carter et al, 2013) demonstrated that relapse following rituximab is associated with an increase in the B cell cytokine BAFF and rising anti-DNA antibodies (a biomarker of disease activity). We hypothesise that rising BAFF levels limit rituximab's efficacy by precipitating flares and that this could be countered by the anti-BAFF therapeutic, belimumab. The aim of this study is to examine the efficacy and safety of this treatment approach.

Design: In order to do this we have designed a double blind, placebo-controlled trial in which we will randomise 50 patients to receive either belimumab or placebo 4-8 weeks after the 1st infusion of B Cell Depletion Therapy (BCDT, Rituximab which has already been administered as standard of care.

Primary outcome measure: Anti-dsDNA antibody levels correspond to disease activity (ie the higher the levels the more active the disease) therefore, the primary outcome measure is anti dsDNA-antibody levels at 52 weeks.

Treatment schedule: The schedule consists of a 52-week treatment period with 4-weekly infusions (extra loading dose at 2 weeks), total of 15 infusions (at Day 0, weeks 2,4,8,12,16,20,24,28,32,36,40,44,48,52
This is then followed with a follow up assessment at Week 56, one month after the end of trial treatment. At Week 68 Female participants will return for pregnancy testing and Male participants will be contacted by their research teams to obtain pregnancy information regarding their female partners. Each participant therefore, will be enrolled on the trial for a total of 68 weeks.

Inclusion criteria:

1. Aged between 18 and 75 years
2. Patients with 4 or more criteria for SLE according to the American College of Rheumatology (ACR) 1997 criteria or SLICC 2012 criteria or biopsy proven lupus nephritis with one additional supportive test on at least two occasions (positive ANA, anti-dsDNA antibodies or anti-Sm antibodies)
3. History of anti-dsDNA antibodies detectable at least once in the past 5 years prior to screening the patient on the study protocol (ELISA test should be used for Anti dsDNA antibody testing).

4. Patients have received the first infusion of this cycle of B cell depletion therapy (Rituximab) 4-8 weeks before randomisation. Previous use of Rituximab is allowed.

5. No contraindications to the use of Belimumab.
6. Ability to provide informed consent

Exclusion criteria:

1. Severe "critical" SLE flare defined as BILAG A flare in CNS system or any SLE manifestation requiring more immunosuppression than allowed within the protocol in the physician's opinion
2. Pregnancy and/or Breast Feeding patients
3. At risk of pregnancy and unwilling to use an acceptable form of birth control contraception (see section 6.3.1.4)
4. Prior use of Belimumab, Atacicept or any biologic therapy (except Rituximab, but no other B cell depleting therapies)
5. Participation in any other interventional trial within the last 6 months
6. eGFR <30mls/min at screening
7. Active infections, including but not limited to:
    i. Current or past infection with hepatitis B or C as defined by:
        A. Hepatitis B surface antigen positive
        B. Hepatitis B surface antibody positive and hepatitis B core antibody positive
        C. Hepatitis C antibody positive
    ii. Historically positive HIV test or test positive at screening for HIV
    iii. Active TB.
8. Infection history:
    i. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
    ii. Hospitalization for treatment of infection within 60 days of Day 0
    iii. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 30 days of Day 0
9. Receipt of a live-attenuated vaccine within 3 months of Day 0 (see participant timeline)
10. In the investigator's opinion, patients that are at high risk for infection (including but not limited to in dwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent severe urinary tract infection)
11. IgG levels below 4.0 g/L, IgA level < 10 mg/dL (IgG and IgA test must be performed no more than 10 days before study drug commenced for the second inclusion/exclusion criteria assessment at week 0)
12. Primary immunodeficiency
13. History of malignant neoplasm within the last 5 years
14. History of cervical dysplasia CIN Grade III cervical high risk human papillomavirus or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS) within the past 3 years. The patient will be eligible after the condition has resolved (e.g., follow-up HPV test is negative or cervical abnormality has been effectively treated >1 year ago)
15. Severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, pulmonary, cardiac, or neurological disease or, in the investigator's opinion, any other concomitant medical

condition or significant abnormal laboratory value that places the participant at risk by participating in this study with the exception of diseases or conditions related to active SLE.

16. Comorbidities currently requiring systemic corticosteroid therapy.
17. Evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgement, pose a significant risk.
18. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
19. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0
20. White blood cells (WBC) <1.5 x 10^9/L, Neutrophils <1 x 10^9/L measured up to 10 days before week 0 (study drug commenced)
21. A history of major organ transplant or hematopoietic stem/cell/marrow transplant or renal transplant.

Concomitant therapy:

The following is a list of concomitant therapies permitted during the BEAT Lupus trial:

- The maximum dose of Mycophenolate after randomization is 1g/day (with a suggested target reduction to 500mg/day at 3 months).
- The maximum dose of azathioprine after randomization is 1mg/kg (with a suggested target reduction to 0.5mg/kg by 3 months).

Azathioprine and Mycophenolate cannot be administered together as a combined regimen. ***No other immunosuppressants are allowed after randomisation.***

- Background anti-malarial drugs are permitted but no new anti-malarials can be started after randomisation. Mepacrine is acceptable for skin problems resistant to Hydroxychloroquine.
- Patients will be permitted to receive up to 20 mg prednisolone/day from randomisation and throughout. It is suggested that prednisolone should be reduced by 50% at 6 months post randomisation. Dose adjustments of prednisolone below 10 mg/day are entirely at the discretion of the treating physician.
- For patients with nephrotic range proteinuria and albumin levels of <20g/l, daily prophylactic low molecular weight heparin, dose adjusted according to renal function, is recommended to reduce the risk of thrombosis.
- For patients with significant proteinuria and albumin ≥ 20g and ≤30g/l, it is recommended that patients are given aspirin 75mg od unless contraindicated. This is also recommended for all patients with anticardiolipin antibodies or positive lupus anticoagulant.
- Treatment of hypogammaglobulinemia in participants with infectious AEs is permitted at the discretion of the site investigator, in consultation with Chief Investigator.

- The use of live-attenuated vaccines is prohibited during treatment with study medications and for 16 weeks after treatment.
- Measures to prevent and to treat osteoporosis are strongly encouraged during this trial. These measures may include: vitamin D (up to 2000 IU/day), and bisphosphonates.
- At the discretion of the site investigator, participants may be treated with a cholesterol-lowering agent such as a statin.
- All participants not already on either an ACE inhibitor (ACEi) or an angiotensin receptor blocker (ARB) may be started on such an agent unless contraindicated. Doses should be adjusted in an attempt to achieve a targeted systolic blood pressure less than 130 mmHg. A combination of medications that may include an ACEi, ARB, calcium channel blocker, or beta-blocker may also be used if a single agent does not control systolic blood pressure adequately.

Patients who flare with one BILAG A or 2 BILAG B scores will be permitted to receive other therapies or increased prednisolone (including intravenous methylprednisolone/above baseline dose of Prednisolone/Mycophenolate/Azathioprine) at the discretion of the treating physician and can also continue with Belimumab or placebo at the discretion of their physician.

Further cycles of Rituximab are not advised during the trial even in the event of a BILAG A or 2 BILAG B flare.