Infliximab versus alpha interferon in the treatment of Behçet's disease: the BIO BEHÇET'S RCT

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Scientific summary

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Background

Behçet syndrome (BS), a multisystem inflammatory vasculitis, is infrequent in the UK, but it has the potential to cause significant morbidity and mortality. The evidence base supporting biologic treatment, which is used for active disease after failure of standard immunosuppression or when prognosis is poor, is largely based on uncontrolled studies. At the time of the trial, the UK National guideline for therapy of Behçet's indicated that either the tumour necrosis factor alpha inhibitor infliximab or the interferon alpha drug Roferon could be employed as treatment for patients following failure of first-line treatment with standard immunomodulators. The Bio Behçet's trial was conceived to exploit the opportunity of the three UK National Centres of Excellence for Behçet's and associated satellite centres to undertake the first randomised clinical trial to compare infliximab and Roferon as treatment for BS, together with an exploratory analysis of potential genomic and metabolomic biomarkers of therapeutic response.

Methods

The Bio Behçet's trial is a pragmatic, standard of care, single-masked, randomised, two-arm, parallel trial comparing the efficacies of infliximab and Roferon employed after failure of first-line therapy in BS. Patients with BS, diagnosed according to the International Study Group 1990 criteria, with active disease who had failed to respond to, or were intolerant of, first-line treatment of BS with topical steroids or small-molecule immunosuppressants were randomised to treatment with either infliximab (Remicade) 5 mg/kg intravenous infusions or Roferon subcutaneous injection (in variable dose), utilising the treatment protocol for each of these drugs in normal clinical care as detailed in the BS drugs pathway for England.

The trial utilised a Bayesian design utilising priors informed by a small survey of international experts in BS. Utilising a Bayesian analysis of covariance model, with an 80% credible interval, a sample size of 45 patients per arm was deemed appropriate and gave a Bayesian power of 90%. Allowing for an anticipated 10% dropout rate, 100 patients were planned to be recruited but reduced to 80 following recommendations to reduce the overall length of the trial. Allowing for a 10% dropout rate, estimates of study power based on 72 evaluable patients (36 on each arm) and an 80% credible interval a Bayesian power of 88% was obtained.

Between June 2016 and February 2020, 161 patients were screened, and 79 patients were randomised. The intention-to-treat analysis was restricted to 37 subjects allocated to infliximab and 37 to Roferon.

Based on previous work with hepatitis C infection and response to interferon therapy and given the role of the innate immune system in the pathogenesis of BS, we examined interferon lambda 3 (IFNL3) and interferon lambda 4 (IFNL4) single nucleotide polymorphisms (SNPs) as biomarkers of response to treatment with alpha interferon and/or infliximab in BS. We also examined the potential for urine metabolomics to act as biomarkers for drug response.

The primary outcome was a modified version of the Behçet's disease activity index (mBDAI) after 3 months of therapy. Secondary outcomes comprised mBDAI score after 6 months of therapy and significant improvement in organ systems after 3 and 6 months (week 12 and week 24 visits) assessed by: reduction in vitreous haze using the SUN consensus group grading scale and best corrected visual acuity change [using the logarithm of the minimal angle of resolution (LogMAR) chart at 4 m] from baseline; change in oral ulcer severity score; change in number of genital ulcers; arthritis pain (10 cm Likert scale); adverse events (AEs) in each group; reduction in dose of prednisolone (or equivalent glucocorticoid) at 3 months

(week 12 visit); reduction in dose of prednisolone (or equivalent glucocorticoid) at 6 months (week 24 visit); quality-of-life (QoL) scores at 3 and 6 months (week 12 and week 24 visits) and Physician's Global Assessment of disease activity at 3 and 6 months (week 12 and week 24 visits).

Results

Baseline characteristics of the two treatment arms did not differ significantly by sex, ethnic profile, baseline disease characteristics and steroid use.

For the primary outcome measure, change in mBDAI between baseline and 3 months (and as a secondary outcome between baseline and 6 months) did not differ significantly between the two treatments [mean difference (80% CrI) = 0.13 (−0.19 to 0.46)].

A significantly higher proportion of patients randomised to Roferon swapped away from their randomised treatment compared to those randomised to infliximab treatment (Roferon 11 of 37, infliximab 3 of 37; $p = 0.0104$).

The clinician's overall perception of disease activity indicated a reduction in disease activity for most patients between baseline and 3 months and between baseline and 6 months, with a median reduction of −2.0 (infliximab) and −1.0 (Roferon) at 3 months and −3.0 (infliximab) and −2.0 (alpha interferon) at 6 months. There was a small but significant difference in favour of infliximab compared to Roferon at both 3 and 6 months ($p < 0.05$).

There were no significant differences between the two treatments at 3 or 6 months for secondary outcome measures, including oral ulcer activity score, genital ulcer activity score and Likert pain score, though, for each of these secondary outcome measures, there were important clinically significant within-group reductions over time at 3 and 6 months. There were no important differences between the two treatments for QoL measures. A modest steroid-sparing effect was observed for each treatment.

In total, 46 patients reported 270 Aes. There were a greater number of AEs observed on Roferon ($p < 0.001$). Eight serious adverse events (SAEs) from five patients were reported across the study. One patient on the infliximab arm reported four SAEs [hypertension (×2), bacterial urinary tract infection and blood pressure inadequately controlled]. In total, three patients (six events) were reported on the infliximab arm, and two patients (two events) were reported on the Roferon arm. There were no suspected drug interactions and no suspected unexpected serious adverse reactions (SUSARS) reported in the study.

The genetic data suggest the possibility of an association between response to treatment and carriage of either rs4803221 or rs7248668 variants in the IFNL3 (interleukin 28B) gene locus only for the alpha interferon-treated arm, in line with association between these two SNPs and Roferon treatment outcome in hepatitis C. These results must be treated with caution due to small numbers in responder subgroups.

There were no baseline differences in metabolomic analysis between the patients before randomisation, indicating no major confounding factors that may have influenced response to a particular treatment. Comparison of 24-week urine samples from responders and non-responders to the same drug using principal component analysis revealed, for infliximab, one specific bin of metabolites that remained significantly different comparing responders to non-responders. This effect was weaker for Roferon, but further study will be required to identify individual metabolites and the associated metabolic pathways responsible for these results.

Conclusion

Using a Bayesian trial design, in this first randomised controlled study comparing infliximab with Roferon when used after primary treatment failure, both were found to be effective and largely equivalent, with minor benefits favouring infliximab in terms of efficacy and tolerability. Mechanistic studies utilising genomics and metabolomics to identify predictors of response to treatment revealed opportunities for further study based on our initial findings. The UK National Behçet's Centres of Excellence and associated satellite centres can be an effective resource to support clinical trials in the management of BS.

Trial registration

This trial is registered as EudraCT Number: 2014-005390-36; ISRCTN49793874.

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