LB01.02 - Phase 2 clinical trial evidence that a retinoid-X receptor agonist promotes remyelination in people with relapsing-remitting multiple sclerosis

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Abstract

Background

Retinoid acid X receptor [RXR] gamma agonists promote oligodendrocyte progenitor cell differentiation and remyelination following experimental demyelination.

Objectives

To assess the safety and efficacy of bexarotene, a non-specific RXR agonist licensed for cutaneous T-cell lymphoma, as a remyelinating therapy in people with relapsing remitting multiple sclerosis.

Methods

In a double-blind, placebo-controlled, phase 2a trial (Cambridge Centre for Myelin Repair: CCMR-One), participants aged 18-50 years with relapsing remitting multiple sclerosis, stable on dimethyl fumarate for at least 6 months, were randomised to bexarotene 300mg/m² or placebo for 6 months. The primary efficacy outcome was change in mean lesional magnetisation transfer ratio (MTR) for lesions whose baseline MTR was below the median lesional MTR for that patient. The secondary efficacy outcome was change in full-field visual evoked potential (VEP) latency in eyes with electrophysiological evidence of optic neuropathy (baseline latency >118ms). We analysed by intention to treat.

Results

52 patients were randomised 1:1 to receive six months of bexarotene or placebo. Two placebo patients withdrew before receiving study drug and one bexarotene patient withdrew consent during the trial. All bexarotene patients experienced adverse effects, notably central hypothyroidism (26 [100%]) and hypertriglyceridaemia (24 [92%, mean maximum of 6.79 mmol/L ,SD 4.4]); as well as rash (13 [50%]) and neutropenia (10 [38%]). Two discontinued placebo because of adverse events and five discontinued bexarotene because of rash [2], neutropenia, triglyceridaemia and mood disturbance. The primary efficacy outcome was negative (mean submedian lesion MTR change was 0.25pu in the bexarotene group versus 0.09pu in the placebo group, \( p=0.54 \)), but in an exploratory, lesion-level analysis, though treatment difference in submedian lesions was too small to achieve significance, it was statistically significantly greater than in supermedian lesions (\( p=0.007 \)). This suggests that bexarotene has a biological effect on MTR and that this effect is dependent on baseline lesional MTR. This interpretation is supported by the finding that bexarotene treatment reduced full field visual evoked potential latency compared to placebo in the
52 eyes with delayed VEPS at baseline, by 4·66 ms/eye (95% CI -8·38 -0·93; p=0·014) and in all eyes, by a per-protocol analysis, by 4.02ms/eye (P=0.015).

Conclusions

Despite a negative primary efficacy outcome, evidence from both magnetisation transfer ratio imaging and visual evoked potentials suggest that a retinoic X receptor agonist, bexarotene, promotes remyelination in people with multiple sclerosis. We have also a heterogeneous response of MS lesions to a drug promoting remyelination. Although bexarotene’s safety profile precludes its widespread use, these data support efforts to develop a selective RXR-gamma agonist.