

## Opicinumab

Ahmed, Zubair; Fulton, Daniel; Douglas, Michael

DOI:

[10.21037/atm.2020.03.131](https://doi.org/10.21037/atm.2020.03.131)

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*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Ahmed, Z, Fulton, D & Douglas, M 2020, 'Opicinumab: is it a potential treatment for multiple sclerosis?', *Annals of Translational Medicine*. <https://doi.org/10.21037/atm.2020.03.131>

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# Opicinumab: is it a potential treatment for multiple sclerosis?

Zubair Ahmed<sup>1</sup>, Daniel Fulton<sup>1</sup>, Michael R. Douglas<sup>1,2,3</sup>

<sup>1</sup>Neuroscience & Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK; <sup>2</sup>School of Life and Health Sciences, Aston University, Birmingham, UK; <sup>3</sup>Department of Neurology, Dudley Group NHS Foundation Trust, Dudley, UK

*Correspondence to:* Zubair Ahmed. Neuroscience & Ophthalmology, Institute of Inflammation and Ageing, Robert Aitken Institute of Clinical Research, University of Birmingham, Birmingham, UK. Email: z.ahmed.1@bham.ac.uk.

*Provenance:* This is an invited article commissioned by the Section Editor Jinming Han, MD (Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden).

*Comment on:* Cadavid D, Mellion M, Hupperts R, *et al.* Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2019;18:845-56.

Submitted Feb 23, 2020. Accepted for publication Mar 05, 2020.

doi: 10.21037/atm.2020.03.131

**View this article at:** <http://dx.doi.org/10.21037/atm.2020.03.131>

Cadavid *et al.* (1) reported the results of the SYNERGY trial using opicinumab, which is a fully humanised anti-LINGO-1 antibody in multiple sclerosis (MS) patients. The study evaluated the clinical safety, efficacy, and pharmacokinetics of four different doses of opicinumab versus placebo added on to intramuscular interferon- $\beta$ 1a over 72 weeks in patients with relapsing MS. However, the findings of the clinical trial did not show a significant dose-linear improvement in disability compared with placebo in patients with relapsing MS.

MS is characterised by chronic central nervous system (CNS) inflammation, demyelination, gliosis and axonal loss resulting in CNS dysfunction and disability (2). Current therapeutic approaches using anti-inflammatory or immunomodulatory agents to reduce inflammatory disease activity (clinical relapses and MRI changes) do not typically impact on pre-existing disability resulting from prior demyelination or axonal loss and are not considered neuro-restorative (3). The production of effective therapeutic agents to restore CNS structure and function remains a significant unmet clinical need and multiple treatment targets are under investigation.

LINGO-1 is a transmembrane cell surface glycoprotein, with roles in oligodendrocyte precursor cell and neuronal biology (4,5). LINGO-1 expression is upregulated in MS lesions and blockade using antagonistic antibodies or genetic deletion results in increased axonal myelination both *in vitro* and in animal models, with amelioration of disease in experimental autoimmune encephalomyelitis

(6,7). Based on these promising preclinical studies, several clinical studies have now trialled opicinumab (also known as BIIB033)—a human aglycosylated monoclonal antibody blocking LINGO-1, in both optic neuritis and MS (1,8-12).

In a first-in-human phase 1 study (of 72 healthy volunteers and 47 patients with MS), serum and cerebrospinal fluid pharmacodynamic data suggested that infused doses of 10 mg/kg or more were likely to result in CNS antibody concentrations similar to those found to be effective in animal models (13). The protocol was well tolerated with no obvious safety signals. No effects were seen on either inflammatory cells or soluble inflammatory mediators (12). RENEW, a phase 2 randomised study (33 treated, 36 placebo), followed the clinical outcomes in patients presenting with acute optic neuritis, examining visual outcomes particularly visual evoked potentials (VEP) and MRI (11). Patients were treated with high dose steroids and six 4-weekly doses of 100 mg/kg opicinumab. Outcomes at 24 weeks found no significant difference between treatment and placebo groups. Despite this disappointing overall outcome, further analyses (8) suggested that a subgroup with relatively greater age (33 years or above) was associated with significantly improved VEP outcomes. Better VEP outcomes were also associated with lower retinal ganglion cell layer/inner plexiform layer thinning.

The recent SYNERGY study (1) applied many of the above methodologies to examine the effects of opicinumab in patients with relapsing MS. This was a

large (419 enrolled) phase 2 study, with patients treated with intramuscular interferon beta-1a in combination with either placebo or a variable dose of opicinumab (3, 10, 30 or 100 mg/kg). Ages varied from 18 to 52 years and disability (EDSS) from 2.0 to 6.0. As before, infusions were performed every 4 weeks, for a total of 19 doses over 72 weeks. Clinical outcome data included measures of disability [EDSS score, T25FW, dominant and non-dominant hand nine-hole peg test (9HPT), and the 3 spaced auditory serial addition test (PASAT-3)] collected 12 weekly. Brain MRI was performed every 4 weeks to week 24, then at weeks 48, 72 and 84. The primary study endpoint was percentage of participants with confirmed improvement in neurophysical or cognitive function over 72 weeks. The secondary endpoint examined the converse-confirmed worsening of neurophysical or cognitive function. A range of exploratory endpoints examined MRI measures (typically changes in brain lesion properties).

With the exception of the 3 mg/kg dose (45 patients), patients were evenly spread across placebo and titrated dosages (92 to 95). Eighty-percent of participants (n=334) completed the study, while the remainder discontinued treatment for a variety of reasons. The treatment was well tolerated throughout, although an unexplained dose-related increase in mean weight was observed in the opicinumab group. The overall study was negative, with no evidence that opicinumab improved disability outcomes. At two doses there was a trend or weak evidence for improvement (10 mg/kg  $P=0.064$ , 30 mg/kg opicinumab  $P=0.022$ ). Similarly, there was no overall effect on confirmed worsening of disability over 72 weeks ( $P=0.53$ ). Close examination of the data suggested that there may be an effect of the 10 mg/kg opicinumab dose in younger patients with a lower burden of disease (typically a shorter disease duration and more favourable MRI parameters). Using a tertiary endpoint overall response score (evaluating a time integrated mix of disability improvement versus worsening), improvements were seen at 24 and 36 weeks, with 10 mg/kg the most significant ( $P=0.0022$  at 24 weeks,  $P=0.0006$  at 32 weeks). The study may suggest that, using this composite measure, particularly in younger patients with earlier disease and more favourable MRI measures, this dosage may be the most therapeutically promising.

Ultimately, however, the trial should be considered negative and the reasons for the apparent failure of this approach are of interest. Problems could relate to trial design (numbers or characteristic of patients recruited, specific clinical outcomes or time frames). Although the

study was superficially large, with 419 enrolled patients, the power of the study was weakened by using four therapeutic doses. Experience with trials of patients with relapsing disease using primarily clinical outcomes (usually phase 3 studies) typically enrol between 700 and 1,000 patients (14). As a consequence, the study may still be underpowered, although other trials of neuroprotective/neurorestorative therapies have used similar approaches, with variable success but usually reproducible findings (particularly using markers of optic nerve structure and visual function) (15). The trial failure may relate to our incomplete understanding of the mechanisms underlying CNS (both axonal and myelin) damage in MS and failure of regeneration and repair. There are several obstacles to the use of antagonistic antibody-based treatments for CNS conditions, particularly poor penetration of antibodies across the blood-brain barrier due to physical size and active efflux of antibodies from the CNS compartment. A wide range of strategies such as genetic re-engineering as a transferrin receptor or insulin receptor monoclonal antibody fusion proteins or using ultrasound to increase blood brain permeability, have been used in preclinical trials to increase CNS penetration.

The failure of the SYNERGY trial to show efficacy in its primary outcomes marks it as the second trial targeting LINGO-1 to report such outcomes. Several contentious issues in the literature may be relevant to this situation. First, LINGO-1 was initially reported to be present at the plasma membrane of cerebellar granule cells, but in a later study this was found not to be the case, with LINGO-1 presenting an intracellular distribution (16). However, this has recently been refuted by Hanf *et al.* (17) who showed that LINGO-1 immunostaining was observed on cortical neurons without permeabilization of the cells. When cells were permeabilised, LINGO-1 immunoreactivity was also present in the cytoplasm, likely representing intracellular trafficking of the protein. The same study reported that the commercially available LINGO-1 antibody used by Meabon *et al.* in 2015 (18) primarily stained intracellular LINGO-1 in cortical neurons. The source of the disparity between these studies may be due to the relative differences in the peptides that were used as the immunogen for the two antibodies, which may recognise different functional epitopes (potentially masked during protein assembly and/or glycosylation) or that different neuronal populations express LINGO-1 differently. Further work is required to address these issues as the specific spatiotemporal localisation of LINGO-1 is crucial to its functional antagonism by a monoclonal antibody. It is particularly

interesting that opicinumab was shown to have unusual binding properties—recognising LINGO-1 through both standard complementarity-determining regions (CDR) and a secondary cryptic light chain framework site which is only revealed upon CDR binding. Binding through the secondary site appears critical to effects on OPC differentiation and myelination *in vitro* (17), which may well not be seen in studies using other anti-LINGO-1 antibodies.

A further issue involves the histological expression of LINGO-1 in MS, with one study reporting its absence in demyelinating MS tissues (19), while a later study directly opposed these observations (20). Finally, it is also not clear how LINGO-1 exhibits its effects on oligodendroglia. One possible explanation contends that LINGO-1 acts *via* the NgR1/75<sup>NTR</sup> receptor complex (21). However, inhibiting NgR1 had no effect on process extension and MBP production in LINGO-1 expressing MO3.13 cells, a human hybrid oligodendroglial cell line (22).

Despite the overall negative outcome, SYNERGY has nonetheless provided useful information on trial design in patients with established MS-related disability. The study confirmed the feasibility and good tolerability of treatment regimens using peripherally infused monoclonal antibody therapies for CNS neuroregeneration. This is particularly critical in view of the relatively poor CNS bioavailability of these agents, requiring high infusion dosages. The study hinted at a more effective dose range—between 10 and 30 mg/kg. Relatively young patients having lower established disability and more benign radiological features may benefit most from opicinumab treatment, most evident at the 10 mg/kg dose. Younger patients may also have higher numbers of oligodendrocyte precursor cells, whilst older patients may have relatively greater areas of established glial scarring and a decline in the function of pro-repair macrophages and microglia (23), with older patients being less amenable to anti-LINGO-1 antagonism.

With multiple apparent discrepancies in the literature, future studies must aim to clarify whether LINGO-1 is localised to the extracellular cell surface, determine if it is present in human MS tissue, and identify the potential partners involved in downstream LINGO-1 signalling. Moreover, it is possible that other leucine-rich repeat (LRR) molecules may compensate for LINGO-1 blockade *in vivo*, particularly in human disease. For example, AMIGO-3 has been shown to be an alternate candidate molecule blocking acute CNS axon regeneration, where LINGO-1 does not change until 10 days after CNS injury (5,24). With further

information, the interpretation and planning of future clinical trials in neuroregeneration, particularly in MS, should be possible with greater confidence of a successful outcome.

## Acknowledgments

None.

## Footnote

*All authors have completed the ICMJE uniform disclosure form and declare:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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