CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS

ABSTRACT

Objective: This study evaluated the efficacy and safety of ATL1102, an antisense oligonucleotide that selectively targets the RNA for human CD49d, the α subunit of very late antigen 4, in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: In a multicenter, double-blind, placebo-controlled randomized phase II trial, 77 patients with RRMS were treated with 200 mg of ATL1102 subcutaneously injected 3 times in the first week and twice weekly for 7 weeks or placebo and monitored for a further 8 weeks. MRI scans were taken at baseline and weeks 4, 8, 12, and 16. The primary endpoint was the cumulative number of new active lesions (either new gadolinium-enhancing T1 lesions or nonenhancing new or enlarging T2 lesions) at weeks 4, 8, and 12.

Results: A total of 72 patients completed the study and 74 intention-to-treat patients were assessed. ATL1102 significantly reduced the cumulative number of new active lesions by 54.4% compared to placebo (mean 3.0 [SD 6.12] vs 6.2 [9.89], p = 0.01). The cumulative number of new gadolinium-enhancing T1 lesions was reduced by 67.9% compared to placebo (p = 0.002). Treatment-emergent adverse events included mild to moderate injection site erythema and decrease in platelet counts that returned to within the normal range after dosing.

Conclusions: In patients with RRMS, ATL1102 significantly reduced disease activity after 8 weeks of treatment and was generally well-tolerated. This trial provides evidence for the first time that antisense oligonucleotides may be used as a therapeutic approach in neuroimmunologic disorders.

Classification: This study provides Class I evidence that for patients with RRMS, the antisense oligonucleotide ATL1102 reduces the number of new active head MRI lesions. Neurology® 2014;83:1780–1788
RNase H leading to degradation of the RNA strand of the RNA:DNA duplex. \(^{5,6}\) ATL1102 selectively reduces CD49d RNA and VLA-4 expression in primary human cells and in several human cell lines and inhibits cell adhesion. ATL1102 is rapidly cleared from the blood after administration and distributes to tissues including lymphoid organs that contain lymphocytes that express VLA-4. The aim of this proof-of-concept trial was to evaluate whether ATL1102 treatment was able to reduce brain lesion activity and to determine its safety profile in patients with RRMS.

**METHODS** ATL1102. ATL1102 is a single-stranded second-generation antisense oligonucleotide designed to hybridize to the 3'-untranslated region of human CD49d RNA. ATL1102 is 20 bases in length, with a molecular weight of 7230 Da. It is the 19-sodium salt of a 3'→5' phosphorothioate oligonucleotide 20-mer with a 3'-9, 2'-O-(2-methoxyethyl) gapmer design to support an RNase H antisense mechanism of action. The ATL1102 sequence is 5'-OMC(C 5'-O-(2-methoxyethyl) gapmer design 3'-G-5' C 5'-O-(2-methoxyethyl) modified and cytosine and uracil bases 5'-methylated (Me).

Study protocol approvals, registrations, and patient consents. The trial is registered with the Australian New Zealand Clinical Trials Registry as trial number ACTRN12608000226303. Written informed consent was obtained from all patients before initiating study-related procedures. The conduct of the trial was approved by each country’s regulatory authority and independent ethics committees of each participating center.

**Trial design.** This phase II trial in patients with RRMS was conducted as a randomized, multicenter, double-blind, placebo-controlled study. The study comprised 3 periods as follows:

1. 2-week screening period (visit V1, day -14 to 0), during which 95 patients were screened;
2. 8-week treatment period involving a 1-week induction phase (visit V2, day 1; visit V3, day 2) where 200 mg of ATL1102 was administered on days 1, 4, and 7 followed by a 7-week maintenance phase (visit V4, day 14; V5, day 28; V6, day 56) with 2 doses of 200 mg ATL1102 administered weekly on days 4 and 7; and an
3. 8-week follow-up period (visits V7, day 84; V8, day 112).

At visit V2, 77 eligible patients were randomly allocated in a ratio of approximately 1:1 to either the ATL1102 group (n = 36) or placebo group (n = 41) as outlined in appendix e-1 on the Neurology® Web site at Neurology.org. Study medication was administered subcutaneously (SC) by the investigator or the patient, blinded to treatment assignment. Each dose of ATL1102 contained 200 mg of ATL1102 in water for injection adjusted to pH 7.4 and was administered as 2 100-mg SC injections.

**Patient inclusion and exclusion criteria.** Male and female patients were eligible for inclusion in the study if they were aged 18–55 years and had RRMS; at least 9 T2 lesions or at least 4 T2 lesions if one was gadolinium (Gd)-enhancing, with at least one relapse in the previous 12 months, but no relapses in the previous 4 weeks; and Expanded Disability Status Scale (EDSS) score 0–6.0. For patients previously treated with immunosuppressive drugs or immunomodulating drugs, there was a 6- or 2-month prestudy washout period, respectively.

Patients were excluded if they were HIV- or HCV-positive or had detectable levels of JC virus in the blood as measured by quantitative PCR.

**Detailed eligibility criteria are available on the Australian New Zealand Clinical Trials Registry, number ACTRN12608000226303.**

**MRI of T1 and T2 lesions.** MRI sites were selected based on successful performance of a dummy run and all in-study scans were subjected to a quality control procedure at the Image Analysis Centre in Amsterdam for central blinded assessment. The MRI protocol included T2-weighted images and T1-weighted images before and after standard-dose Gd. Five MRI scans were performed per patient and were taken at baseline (between day -14 and -7), week 4 (after 9 doses), week 8 (after 17 doses), week 12, and week 16. In case of relapse, an additional MRI scan was performed.

The following MRI efficacy assessment was done by an experienced reader blinded to treatment allocation:

- Number of new T1 Gd-enhancing lesions indicating blood–brain barrier disruption
- Number of new/enlarging T2 hyperintense lesions
- Total volume of enhancing lesions

Scans were also reviewed by a board-certified neuroradiologist for progressive multifocal leukoencephalopathy (PML) independently of the team assessing the scans for efficacy.

**Efficacy assessments.** The primary objective of this trial was to evaluate whether ATL1102 treatment was able to reduce brain lesion activity compared to placebo in patients with RRMS and Class I evidence is provided. The primary efficacy endpoint was the cumulative number of new active lesions (either new T1 Gd lesions or nonenhancing, new, or enlargeting T2 lesions) on MRIs at weeks 4, 8, and 12 compared to placebo-treated patients.

A secondary efficacy endpoint was the cumulative volume of all T1 Gd lesions on MRIs at weeks 4, 8, and 12 in the ATL1102 compared to placebo-treated patients.

Additional assessments included the cumulative number of T1 Gd lesions on MRIs taken at weeks 4, 8, and 12, and in a post hoc analysis, the cumulative number of new T1 Gd lesions at weeks 4, 8, and 12 in the ATL1102-treated patients compared to placebo. Also assessed were the total number of multiple sclerosis (MS) relapses, the total number of patients with no relapse, and the EDSS.

**Safety data.** Safety was evaluated on the basis of adverse events, laboratory data, vital signs, MRI assessment for PML, physical examination, 12-lead ECG, and local tolerance. Adverse events were reported by the patient or noted by the investigator over the entire study period.

**Statistical procedures.** Efficacy analyses were carried out for the intention-to-treat (ITT) population (randomized patients who received at least one injection of study medication, had a valid baseline MRI scan, and, at least one valid postbaseline MRI scan), the ITT subset population (patients with valid pretreatment MRI brain lesion counts at weeks 4, 8, and 12), and the per-protocol (PP) population (patients with no major protocol violations).

The primary efficacy variable (cumulative number of new active lesions on MRI at weeks 4, 8, and 12) was analyzed using a negative binomial regression model. The secondary
variable (cumulative volume of T1 Gd lesions on MRI at weeks 4, 8, and 12) was analyzed using a nonparametric rank analysis of covariance model. The primary and secondary efficacy analyses used treatment, sex, and country (pooled centres) as factors, and age and number or volume of enhancing lesions on screening MRI as covariates, respectively. One-sided $p$-values, point estimates, and 2-sided 90% confidence intervals (CIs) for the differences between treatment groups were determined. For the primary efficacy analysis, a 1-sided significance level of 0.05 was specified in the study protocol. The sample size justification and powering are outlined in appendix e-1.

Missing MRI data due to causes other than relapse were replaced by the median lesion count of all new active lesions on MRIs taken at the same planned week for all patients within the same treatment group. Of the patients in the ITT population, 2 patients in the placebo group had one missing postbaseline scan each and one patient in the ATL1102 group had 3 missing scans postbaseline scan, all for reasons other than relapse.

RESULTS Study patients and conduct. Of the 95 patients screened, 77 were randomized and treated with study medications. The patient demographic data were summarized for each treatment group (table 1). Overall, the treatment groups were well-balanced with respect to demographic data. There were no clinically relevant differences with previous or concomitant medical conditions or medications. The median duration of history of MS prior to enrollment was lower in the placebo group (1.8 years, range 0.0–15.7) than in the ATL1102 group (3.0 years, range 0.0–25.8).

Five patients withdrew prematurely and 72 completed the study. Patients who discontinued the study still underwent the final examinations. The ITT population consisted of 74 patients, the ITT subset 71 patients, and the PP population 68 patients (figure 1). The mean (SD) duration of study medication in the randomized population was slightly higher in the placebo group, 55 (7.06) days, compared to ATL1102 group, 53.3 (9.32) days.

Efficacy. The cumulative number of new active lesions for weeks 4, 8, and 12 (primary outcome measure) was 54.4% lower in the ATL1102 group than in the placebo group (figure 2A); mean (SD) number of new active lesions 3.0 (6.12) vs 6.2 (9.89), 1-sided
$p$ value 0.0050 (90% CI 1.2855, −0.2840) (ITT population). A significant difference between the 2 treatment groups was present at the end of the active treatment phase (week 8); mean (SD) number of new active lesions 2.6 (5.75) vs 3.6 (5.49), 1-sided $p$ value 0.0456 (90% CI 2.1005, 2.0133) (ITT population). Similar results were found in the ITT subset and PP populations.

The cumulative T1 Gd lesion volume for weeks 4, 8, and 12 (secondary outcome measure) was lower in the ATL1102 group than the placebo group: 358 (1,028.4) mm$^3$ vs 589 (1,107.6) mm$^3$, with a clear trend towards significance (1-sided $p$ value 0.0534 (90% CI −0.129, 12.863). ATL1102 significantly reduced T1 Gd lesion volume by 84.4% at week 12 compared to placebo (2-sided $p = 0.0172$; Wilcoxon 2-sample test) (figure 3A).

ATL1102 reduced the cumulative number of T1 Gd lesions for weeks 4, 8, and 12 by 66.7% compared to placebo, mean (SD) 2.9 (7.92) vs 6.1 (11.13), 1-sided $p$ value 0.0010 (ITT) (figure 3B), and reduced the cumulative number of new T1 Gd lesions for weeks 4, 8, and 12 by 67.9% compared to placebo, mean (SD) 2.1 (7.92) vs 6.1 (11.13), 1-sided $p$ value 0.0008 (ITT) (figure e-1A). Notably, ATL1102 significantly reduced T1 Gd and new T1 Gd lesion numbers by 88.5% and 90.5%, respectively, at week 12 compared to placebo (2-sided $p = 0.010$ and 0.005, respectively; Wilcoxon 2-sample test) (figure 3B and e-1B).
ATL1102 treatment led to an absolute increase of 24.8% ($p = 0.0332$) and relative increase of 51% (risk reduction = 73.5/48.7 = 1.51) in the percentage of T1 Gd lesion-free patients compared to placebo measured at 8 and 12 weeks combined ($\chi^2$, figure 4).

The number of patients with MS relapses in the 2 treatment groups were 8 (19.5%) patients in the placebo group vs 6 (16.7%) patients in the ATL1102 group; however, the difference did not reach significance. Mean EDSS scores decreased slightly during the study in both groups but the difference between the groups was not statistically significant. Frequencies of patients with increases or decreases in EDSS were comparable in the 2 treatment groups.

**Safety.** The most common treatment-emergent adverse events (TEAEs) in the ATL1102 group were injection site erythema (25.0% patients), alanine aminotransferase (ALAT) increases (19.4%), MS relapses (16.7%), aspartate aminotransferase increases (11.1%), headache (11.1%), and thrombocytopenia (22.2%) (table e-1). MS relapse was the most frequent TEAE in the placebo group (19.5% patients). Injection site erythema, ALAT increases, and thrombocytopenia were more frequent in the ATL1102 group than in the placebo group (difference ≥5%). Serious TEAEs were MS relapses and one case of grade 2 thrombocytopenia in the ATL1102 group. No JC virus in the blood or PML was observed.
**DISCUSSION** The ATL1102 trial conducted in patients with RRMS met its primary efficacy endpoint, reducing cumulative number of new active lesions at weeks 4, 8, and 12 by 54% vs placebo after 8 weeks of dosing and the cumulative number of new T1 Gd lesions by 67.9% vs placebo.

Treatment of patients with RRMS with natalizumab with 2 injections over 2 months resulted in reductions in the cumulative number of new active lesions over 12 weeks of 50% vs placebo and the cumulative number of new T1 Gd lesions by 52% vs placebo. Treatment of patients with MS with other drugs registered for RRMS have shown reductions in brain lesions over the first 12-week treatment period, albeit with different, generally lower, levels of activity. Pairwise meta-analysis comparisons between marketed treatments in longer randomized controlled trials indicate that natalizumab may have better relative effectiveness on the parameters of "patients without MRI progression" and "patients free of relapse." ATL1102 demonstrated an increasing effect over time with T1 Gd lesion reductions by week 8 and the greatest T1 Gd lesion reductions observed at week 12, 4 weeks after the last dose. This extended duration of activity postdosing of ATL1102 was potentially related to the time course for the formation-turnover of new enhancing lesions and the drug’s long (>3 weeks) tissue half-life. The extended duration of action supports the proposition of less frequent or lower dosing in longer-term studies than the twice-weekly 200-mg dosing employed in the current trial. Pharmacometric modeling suggests 200 mg once
weekly, every other week, and every 3 weeks over 6 months has the potential to significantly reduce MRI brain lesions and to minimize side effects including platelet reductions. This dosing schedule could be employed in longer-term clinical trials.

TEAEs with a frequency of more than 10% in the ATL1102 group vs a lower frequency (difference of >5%) in the placebo group were mild to moderate injection site erythema, mild increases in liver enzyme ALAT, and a decrease in platelet count that was reversible after treatment interruption and not accompanied by any clinical consequences.

There were fewer patients with relapses in the ATL1102 group; however, this study was not powered to detect significant differences in relapses or neurologic disability as assessed by the EDSS, the view being that longer duration and larger studies are needed to see changes in these clinical parameters.

ATL1102, like other antisense oligonucleotides of the same class, has a short half-life of 4.8 hours in the blood. There was no significant change in blood leukocyte CD49d RNA levels with ATL1102, which may reflect the short exposure of these cells to ATL1102 in the blood and poor cellular uptake. Animal studies have shown that like other antisense drugs, ATL1102 distributes rapidly to the bone marrow, spleen, and lymph nodes in relatively high drug concentrations. An antisense fully complementary to murine CD49d RNA reduced VLA-4 expression in inflamed lymph nodes and spleen. Accordingly, ATL1102 may be reducing CD49d RNA and VLA-4 expression on immune cells in these lymphoid tissues in patients with RRMS. Supporting this hypothesis, ATL1102 treatment produced a ~10% reduction in the number of CD19+ (pre) B cells with detectable levels of VLA-4 expression in the blood at 8 weeks (appendix e-2). A small number of leukocytes are known to migrate from the secondary lymphoid tissues via the blood, which may be the source of these VLA-4-negative CD19+ cells in the blood.

ATL1102 treatment reduced the number of circulating CD19+ (pre) B cells (53%) and granulocytes (43%) at 8 weeks compared to treatment with placebo; T cells were less significantly reduced (~25%), but ATL1102 treatment had no effect on monocyte or NK lymphocyte numbers (appendix e-2). VLA-4 has a role in the maturation, apoptosis, activation, adhesion, and migration of B and T cells. ATL1102 may be having an effect on one or more of these activities on CD19+ (pre) B and T cells within the lymphoid tissues of patients with RRMS, thereby reducing leukocyte number and activity in blood, and in turn the CNS, and subsequently reducing the number and volume of MS brain lesions in this RRMS study.

Natalizumab interferes with transmigration of VLA-4+ leukocytes and disproportionately increases circulating B cells more than other lymphocytes and monocytes in blood of patients with RRMS. The 44% of disease-free natalizumab-treated patients with...
RRMS are characterized by a substantial reduction of CD19+ B cells, particularly the CD5+ subset, and plasmablasts in the CNS. The therapeutic effects of CD20 antibodies that deplete CD20+ blood B cells also point to the importance of reducing proinflammatory B cells in CNS in RRMS.

More analysis is required to characterize the pharmacologic and pharmacodynamic action of ATL1102. Natalizumab increases the release of CD34+ hematopoietic stem/progenitor cells and CD19+ pre B cells and CD20+ B cells into the blood, which carry latent low copy JC virus, including in individuals who are seronegative. Latent JC virus activation is theorized to involve B-cell differentiation, including B-cell DNA-binding protein Spi-B, which increases JCV transcripion. Natalizumab has a long half-life in the blood (6 days), and a broad VLA-4 antagonist effect, and can impair JC virus immunosurveillance, leading to PML.

Preliminary data have shown ATL1102 treatment increases CD34+ RNA 50% at week 8 vs baseline, though its effects at the CD34+ cell level need to be explored (appendix e-2). The reduction of CD19+ (pre) B cells with ATL1102 treatment suggests that release of lymphoid precursors into the blood may be low or they do not survive, potentially reducing the pool of cells that may carry latent virus. ATL1102 does not bind cell surface VLA-4. Natalizumab binding to VLA-4 induces intracellular signaling–associated proinflammatory effects, leading to poor outcomes in patients with PML following treatment suspension. The short ATL1102 half-life in plasma of 4.8 hours potentially limits exposure of circulating leukocytes to drug, which may better preserve blood leukocyte VLA-4–mediated immunosurveillance and therefore be at less risk of causing PML. IFN-β1 treatment of RRMS reduces blood mononuclear cell CD49d RNA and VLA-4 expression on CD8+ lymphocytes and CD4+CD45RO+ primed memory T cells, while preserving other blood leukocyte VLA-4 function. IFN-β1 has not been associated with PML.

ATL1102, which employs a unique antisense mechanism to reduce VLA-4 expression, has in this study substantially reduced disease activity in RRMS at doses that are generally well-tolerated. Longer-term trials are required to confirm its potential as a valuable additional therapeutic option in the treatment of RRMS.

AUTHOR CONTRIBUTIONS

V. Limmoth was the study Principal Investigator and a member of the protocol development team, took primary responsibility for the safety oversight of the study, and revised the manuscript. F. Barkhof was a member of the protocol development team, advised on statistical aspects of the study, and revised the manuscript. N. Desem was a member of the protocol development team, managed day-to-day activities of the study, participated in the safety monitoring process, oversaw the analysis of the data, including the statistical work on the primary and secondary efficacy endpoints carried out by the Accovion GmbH Marburg Germany statistical analysis team and reporting of the study, and contributed to the writing of the manuscript. M.P. Diamond was a member of the protocol development team and contributed to the analysis of the data and the writing of the manuscript. G. Tachas was a member of the protocol development team, contributed to the analysis and interpretation of the data, oversaw the analysis of the statistical work on the additional and post hoc analyses carried out by the statistical analysis team of the McCloud Consulting Group, Sydney, Australia, and performed the primary writing of the manuscript.

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DISCLOSURE

V. Limmoth has received payment for services from the sponsor for consultancy. The Department of Neurology (Dr. Limmoth), Cologne City Hospitals, University of Cologne, Germany, has received compensation for participation in the clinical trial. F. Barkhof has received payment for services from the sponsor for consultancy. The Department of Radiology (Dr. Barkhof), VU Medical Centre, Amsterdam, the Netherlands, has received compensation for participation in the clinical trial. N. Desem holds an equity interest in the sponsor. N. Desem holds an equity interest in the sponsor. G. Tachas holds an equity interest in the sponsor. Go to Neurology.org for full disclosures.

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CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS
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INFLUENZA VACCINATION AND CARDIOVASCULAR RISK IN PATIENTS WITH RECENT TIA AND STROKE

Bayzidur Rahman, Anita Heywood, Aye Moa, C. Raina MacIntyre, Sydney, Australia: Lavallée et al. 1 found no effect of influenza vaccination on risk of cardiovascular disease in recent TIA or stroke patients. Vaccination status was determined by baseline self-report, which has poor validity and is subject to recall bias. 2 This can result in misclassification of vaccination status and bias of the reported effect.

Vaccination timing was not presented in the 3 component studies. Survival analysis was conducted on a baseline vaccination status for any cardiovascular event occurring during the 2-year follow-up. Without annual vaccination data, it is unknown whether participants were protected by vaccination at the time of subsequent cardiovascular events.

The pooling of data from 3 separate studies for the main analyses is not ideal. The analyses should appropriately consider between-study variation (e.g., individual patient data meta-analysis). 3 Two of the component studies (OPTIC and PERFORM) were multicentered (clustered), which also warrants consideration. This study failed to show an unbiased effect of vaccination on cardiovascular events, which conflicts with data showing such an effect. 4,5

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CORRECTIONS

MRI measurement of brain iron in patients with restless legs syndrome

In the article “MRI measurement of brain iron in patients with restless legs syndrome” by R.P. Allen et al. (Neurology® 2001;56:263–265), there is an error in the author byline. The third author’s name should read “F.W. Wehrli, PhD.”

Child Neurology: PRRT2-associated movement disorders and differential diagnoses

In the article “Child Neurology: PRRT2-associated movement disorders and differential diagnoses” by D. Ebrahimi-Fakhari et al. (Neurology® 2014;83:1680–1683), there is an error in the footnote under table 1. Table 1 is not reproduced from Gupta and Lang but was created by the authors. Supplemental table e-2 was modified from Gupta and Lang (Gupta A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2009;22:430–436), with permission. The authors regret the error.

CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS

In the article “CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS” by V. Limmroth et al. (Neurology® 2014;83:1780–1788), there is an error in the Acknowledgment section: “Prof. Krzyzewski” should read “Prof. Selmaq” and “Dr. Strangez” should read “Dr. Stangel.” In addition, the first sentence in the Methods under “Safety data” should read: “Safety was evaluated by an independent data safety monitoring board on the basis of adverse events, laboratory data, vital signs, MRI assessment for PML, physical examination, 12-lead ECG, and local tolerance.” The authors regret the errors.