Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: http://www.tandfonline.com/loi/iafd20

ALSUntangled 45: Antiretrovirals

The ALSUntangled Group

To cite this article: The ALSUntangled Group (2018): ALSUntangled 45: Antiretrovirals, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2018.1465248

To link to this article: https://doi.org/10.1080/21678421.2018.1465248

Published online: 25 Apr 2018.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018; 1–5

RESEARCH ARTICLE

ALSUntangled 45: Antiretrovirals

THE ALSUNTANGLED GROUP

ALSUntangled reviews alternative therapies on behalf of persons with ALS (PALS). In our previous publication "The Rife Machine and retroviruses", we briefly discussed the evidence for a role of retroviruses in ALS (1). Here, we review the use of a class of medications called antiretrovirals (ARVs) for treating ALS, a topic for which we have had over 1400 requests (2).

Overview

Retroviruses are a family of RNA viruses defined by their ability to integrate themselves into the host cell DNA. This feature makes it challenging to eliminate them. Retroviruses acquired by infection are known as exogenous retroviruses. In comparison, endogenous retroviruses have integrated themselves into germline DNA many generations ago and as such are inherited from generation to generation. ARVs are a class of drugs developed for use against viral replication and cell infection by human immunodeficiency virus (HIV), an exogenous retrovirus that is the cause of AIDS.

Mechanisms

Retroviruses are associated with a broad spectrum of neurological disorders (3–9). HIV has been associated with an ALS-like motor neuron disease in over 30 patients (3–6). Another exogenous retrovirus, named Human T-Cell Leukemia Virus type 1 (HTLV-1), causes "HTLV-1 associated myelopathy/tropical spastic paraparesis," which has substantial overlap of clinical features with ALS (5,8). While treatment of HIV-associated ALS-like syndromes with ARVs can sometimes lead to stabilization or remission of the ALS-like symptoms (5,6), to date no ARVs have been shown to be useful in treating HTLV-associated myelopathy (9).

Some PALS without HIV or HTLV infection have detectable activity of an enzyme used by retroviruses called reverse transcriptase (RT; 5,10). Either an unknown exogenous retrovirus or a type of human endogenous retrovirus (HERV) could be the source of this RT activity. One study investigated RT activity in PALS and their family members. The results showed that ∼47% of PALS, ∼13% of spouses of PALS, ∼43% of healthy blood relatives of PALS, and ∼21% of non-related healthy control participants had detectable RT activity. Because the percent of PALS positive for RT activity was similar to blood relatives, but not to spouses, this suggests an endogenous genetic source of the RT activity, i.e. a HERV, and not an exogenous retrovirus acquired through infection (10).

PALS have been reported to have higher HERV expression in muscle and brain (5,11) and higher levels of certain anti-HERV (type K) antibodies relative to controls (12). There are at least two possible explanations for this. First, neuroinflammation in PALS may activate HERV expression. In some PALS, there is activation of the nuclear factor-κB (NF-κB) pro-inflammatory cellular pathway (13–15). Activation of the NF-κB pathway can cause expression of HERV genes *in vitro* (15,16), and, in neurons of PALS, increased protein levels of HERV RT correlate with increased NF-κB levels (15). The second possibility is that HERV protein levels are mediated by TAR DNA binding protein 43 (TDP-43), which has an important role in ALS pathophysiology (17) and has been shown to be increased in the cerebrospinal fluid (18–22) and

ALSUntangled Reviewers who contributed to this paper include the following: Jesse Crayle (lead author), Richard Bedlack (senior author), Carmel Armon, Paul Barkhaus, Michael Benatar, Tulio Bertorini, Mark Bromberg, Greg Carter, Jonathan D. Glass, Daniel Harrison, Terry Heiman-Patterson, Pamela Kittrell, Christopher McDermott, Sabrina Paganoni, Larry Phillips, Erik Pioro, Jeffery D. Rothstein, Kristiana Salmon, Hemangi Sane, Eric N. Valor, Fernando Vieira, and Paul Wicks. Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.
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ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2018.1465248

blood (23) of some PALS. Based on experiments in cultured human cells, *Drosophila* (fruit fly) and mice TDP-43 models, it is possible that HERV RT protein levels are being increased by TDP-43 through a not yet clear mechanism (11,24–26). Interestingly, HIV infection of the CNS also leads to neuroinflammation, increased TDP-43 expression, and increased HERV expression (27).

Regardless of the cause of increased HERV expression, it is still not clear if HERV is contributing to ALS pathology or is simply a byproduct. HERV expression is also increased in a number of other neurological (7,28,29) and non-neurological diseases, such as cancer (30). Furthermore, some think that HERVs may play beneficial roles in the pathophysiology of certain diseases (31); however, this may not be the case in all diseases as research on multiple sclerosis has suggested a pathogenic role for HERVs (32,33).

One recent study provided multiple lines of evidence that expression of a HERV (type K) might cause human motor neuron disease (11). First, the research group showed that HERV full virus or HERV envelope protein (Env) expression is toxic to iPSC-derived human neurons. Second, they created mice that expressed HERV Env in neurons at high levels. These mice had decreased counts of upper and lower motor neurons and developed a disease characterized by progressive muscle weakness with clinical features and muscle biopsy findings similar to human ALS (11). However, these findings are not entirely consistent with prior studies that found HERV Env expression in a human neuroblastoma cell line increased expression of neuronal growth factors and was protective against some neurotoxins in a mouse neuroblastoma cell line (34). These discrepancies could be due to the use of different cell lines, use of slightly different HERV type K Env proteins, or use of different experimental methods to judge cellular injury. These results will need to be independently replicated.

Although there is substantial evidence that HERV expression is increased in PALS (5,11) and pathological in-cell culture and mouse models (11), the use of ARVs against HERVs is postulated on the possibility that a HERV is actively replicating to produce infectious viral particles, i.e. ARVs are lifecycle inhibitors and not inhibitors of gene expression. To-date, there have been two HERVs discovered in the human genome that appear to be potentially able to produce infectious virions (35,36) of which one (36) so-far has been experimentally confirmed to be capable of generating infectious virions (37).

Given that currently available ARVs were developed for use in HIV infection, it is important to assess their ability to inhibit the HERV lifecycle. The current evidence, taken from *in vitro* studies, suggests that HERV type K is susceptible to most members of a class of ARVs called nucleoside reverse transcriptase inhibitors (NRTIs; 38,39), but is relatively resistant to ARVs from the class protease inhibitors (PIs; 38–41). Evidence for *in vitro* efficacy of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors (INSTIs) is mixed (38,39).

If infectious virions are not produced, but it is the expression of HERV proteins themselves that is deleterious, then the best therapeutic would be an interfering RNA, CRISPR gene editing, or another mechanism to block HERV gene expression. Indeed, some think that it is the Env protein of HERV itself that is neuropathogenic (11,42) similarly to what research on other retroviral Env proteins has shown (42,43). There are currently efforts to develop an antibody that specifically targets HERV Env (44), which could also potentially be able to block viral cell infection (45).

In summary of "mechanisms," we found evidence of HERV expression in ALS and that some ARVs are effective against the HERV lifecycle, but it still remains to be determined if suppression of HERV expression and/or viral replication and cell infection are mechanisms that are relevant to achieving a positive therapeutic outcome in PALS, especially as HERV expression seems beneficial in some diseases (31). Based on this evidence, ALSUntangled assigns a TOE "mechanisms" grade of D (Table 1).

Table 1. Table of evidence.

	Grade	Explanation
Mechanism	D	ARVs are effective against some aspects of the retroviral lifecycle, but it is unknown if ARVs will lead to a positive outcome in ALS pathophysiology.
Pre-Clinical	C	One flawed pre-clinical study with a *Drosophila* model of ALS reported some benefit with ARVs of the NRTI class.
Cases	U	We found no cases of PALS using ARVs.
Trials	F	Two published trials in PALS, each using a different ARV in monotherapy, showed no benefit.
Risks	U	Experience of ARVs in PALS is limited. The side effect profile will vary by the specific ARV(s) used.

Pre-clinical models

In a *Drosophila* model of ALS expressing human TDP-43 (hTDP-43) (46), the transgenic fruit flies have progressive neurological degeneration characterized by brain cell death, progressive motor impairment, and a substantially reduced lifespan (25,46). Using this model, one group found that hTDP-43 selectively expressed in the flies' glial cells, but not when selectively expressed in neurons, caused a *Drosophila* endogenous retrovirus similar to HERV type K, named *gypsy*, to be expressed in

higher quantities. In flies with hTDP-43 expressing glia, inhibition of *gypsy* expression by interfering RNA caused the flies to have a lifespan approximately 75% of normal flies, which is an approximately 5-fold increase in lifespan relative to negative control hTDP-43 flies and untreated hTDP-43 flies, which had lifespans approximately 15% of normal flies. Treatment of the same type of hTDP-43 fly with each of the antiretroviral NRTIs stavudine and zidovudine resulted in a small statistically significant increase in lifespan relative to untreated controls (25). This study was well-designed with negative controls, but the meaning of these results to human ALS is difficult to interpret, because they are based on an analog endogenous retrovirus in a non-vertebrate animal and utilized small experimental groups of 6–12 flies. Based on this single study that utilized a *Drosophila* model of ALS to show a small benefit of ARVs, ALSUntangled assigns a TOE "pre-clinical models" grade of C (Table 1).

Cases

As we discussed in "mechanisms", there have been a number of cases of an ALS-like disease in individuals that tested positive for HIV, took ARVs, and recovered some or all motor function (5,6). We know of no cases of PALS that tested negative for HIV and HTLV and improved on a regimen containing ARVs. In the online community PatientsLikeMe, no PALS report taking ARVs (47). Based on this lack of information, ALSUntangled assigns a TOE "cases" grade of U (Table 1).

Trials

There have been two published trials using ARVs in PALS. The first trial was an open-label pilot trial in which 10 PALS each took the NRTI zidovudine between 2 and 12 months. While serum creatine kinase (total CK) levels dropped coincident with treatment, "clinical courses were not significantly altered" (48). This trial utilized an ARV that has excellent penetrance into the CNS (49) and has been reported to be active *in vitro* against HERV (38,39); however, the trial design was flawed in that it enrolled a very small number of PALS, followed them for variable amounts of time, and used unclear clinical outcome measures.

The second ARV trial was a double-blind trial that randomized 46 PALS to either the protease inhibitor indinavir or placebo for 9 months. The study measured ALSFRS scores, muscle strength (MMT composite score), and respiratory function (FVC) at baseline, 3, 6, and 9 months. The results showed that there were no significant differences in the rate of progression between the indinavir group and the placebo group for each of the three outcome measures (50). This study was probably underpowered and may have failed to show an effect because indinavir does not have good potency and efficacy against HERV (38–41) even though it does penetrate the CNS well (49).

It is possible that both of these monotherapy drug trials failed because combination ARV therapy, as is commonly used in HIV care, is necessary to achieve clinically meaningful effects in PALS. We found two open-label pilot trials of triple ARV therapy in PALS that have not yet been published (51,52). Based on the two published trials to-date, ALSUntangled assigns a TOE "trials" grade of F.

Risks

The effect of HERV inhibition on disease progression of PALS is unknown. Both above-mentioned clinical trials in PALS suggested that the side effect profile of two different ARVs in monotherapy is similar between PALS and patients with HIV (48,50); but it is unknown if this extends to other ARVs. In the zidovudine trial, none of the 12 PALS discontinued treatment due to side effects; however, it was not reported if there were any side effects experienced by these PALS (48). Common side effects experienced by patients taking zidovudine for HIV infection include headache, malaise, anorexia, nausea, and vomiting (53). On PatientsLikeMe, >70% of patients reporting their side effect burden with zidovudine reported side effects (54). In the indinavir trial, 4 of 23 PALS taking indinavir had nephrolithiasis with 2 requiring hospitalization. Other symptoms reported by PALS included distortions of taste and gastrointestinal symptoms such as nausea, diarrhea, and indigestion (50). This side effect profile is similar to that experienced by patients with HIV infection (50,55). At least two-thirds of all patients on PatientsLikeMe that have taken indinavir report discontinuing indinavir because of side effects (56). Newer combination ARV therapies, such as Triumeq (57) and Genvoya (58), have a less severe side effect profile in patients with HIV compared with older ARVs. On PatientsLikeMe, for both Triumeq (59) and Genvoya (60), ~50% of patients reporting their side effect burden had no side effects and ~50% had only minor side effects. Based on the general lack of experience in PALS and the highly variable risk profile between different ARVs, ALSUntangled assigns a TOE "risks" grade of U for ARVs overall (Table 1).

Dosing and costs

Antiretrovirals are typically taken by mouth; timing and amount of dosing varies by specific ARVs. Presumably, a retrovirus contributing to ALS pathology acts in the CNS, so an effective ARV therapy

should have adequate CNS penetrance. Additionally, the specific ARV used would need to have activity against the retrovirus targeted and the retrovirus would need to be actively producing infectious viral particles. If targeting HERV type K would be beneficial in PALS, which is still unknown, then a reasonable regimen might consist of two NRTIs and one INSTI given the data above (38–41). The cost of the specific ARV regimen would depend on the drug(s) selected. Triumeq and Genvoya are once-daily pills that each consist of two NRTIs and one INSTI. Each of these combination ARV therapy medications cost roughly $3000 for a one-month supply (61,62). There are less expensive alternatives to these once-daily pills, but these alternatives require complex dose timing and a number of pills that has historically made it difficult for patients to achieve perfect compliance.

Conclusions

Antiretrovirals are a group of diverse drugs developed for HIV infections that vary widely in theoretical efficacy against HERVs, side effect profiles, and cost. HERV expression is apparently increased in some PALS; however, it is unknown if this is a beneficial, neutral, or pathological process. Furthermore, it is not clear if ARV-targeted mechanisms such as cell infection and viral replication are taking place in PALS. Based on the lack of evidence for use of ARVs in PALS who test negative for HIV and HTLV, we cannot recommend them as a treatment for ALS. We look forward to the results of the two ongoing trials of ARVs in PALS.

Declaration of interest

ALSUntangled is sponsored by the ALS Association and the Motor Neurone Disease Association. Richard Bedlack has research support from ALSA, MNDA, Cytokinetics, Neuraltus, and GSK, and consulting support from ALSA, Avanir, Neuraltus, Ultragenyx, Cytokinetics, Mallinkrodt, and Brainstorm Cell. Paul Wicks (PW) is an employee of PatientsLikeMe and holds stock options in the company. PW is an associate editor at the Journal of Medical Internet Research and is on the Editorial Boards of The BMJ and BMC Medicine. The PatientsLikeMe Research Team has received research funding (including conference support and consulting fees) from Abbvie, Accorda, Actelion, Alexion, Amgen, AstraZeneca, Avanir, Biogen, Boehringer Ingelheim, Celgene, EMD, Genentech, Genzyme, Janssen, Johnson & Johnson, Merck, Neuraltus, Novartis, Otsuka, Permobil, Pfizer, Sanofi, Shire, Takeda, Teva, and UCB. The PatientsLikeMe R&D team has received research grant funding from Kaiser Permanente, the Robert Wood Johnson Foundation, Sage Bionetworks, The AKU Society, and the University of Maryland. PW has received speaker fees from Bayer and honoraria from Roche, ARISLA, AMIA, IMI, PSI, and the BMJ.

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