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The ALSUntangled Group

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RESEARCH ARTICLE

ALSUntangled 58: Azathioprine

THE ALSUNTANGLED GROUP

ALSUntangled reviews alternative and off-label treatments for ALS on behalf of patients with ALS (PALS). Here we review azathioprine (AZA), for which we have had over **400** requests (1).

Background

AZA is a prescription medication that suppresses the immune system (2). It works by blocking purine synthesis, which is necessary for DNA production. Cells that are rapidly dividing, such as those of the immune system, are most affected when DNA replication is interrupted (3,4). In the USA, AZA is approved for preventing rejection after kidney transplant and for treating rheumatoid arthritis (3). Numerous off-label uses include as an anti-rejection drug in other organ transplants, in inflammatory bowel diseases, myasthenia gravis, inflammatory muscle diseases, and other immune-mediated diseases (3).

Mechanism

There is evidence suggesting that neuroinflammation is involved in the progression of ALS, particularly via the nuclear factor-κB (NF-κB) cellular signaling pathway (5). This pathway is a regulator of inflammation and is involved in the expression of proinflammatory genes (6). Within microglia, activation of the NF-κB signaling pathways leads to production of inflammatory cytokines which, in turn, leads to increased neuronal cell death (7). NF-κB activity is increased in patients with sporadic ALS and in the SOD1-G93A mouse, and activated microglia are found in the motor cortex and spinal cord of PALS; in mouse models, reducing expression of NF-κB in microglia can slow disease progression (8–10). AZA treatment reduces NF-κB in a mouse model of ulcerative colitis (11), so theoretically it might do the same in PALS. Even if it does, however, it is not clear that this will slow ALS progression. There have been multiple trials involving immunomodulatory drugs, acting at different points in the inflammatory pathway, and to date, none have proven successful (12), although there is ongoing work with masitinib (13) and other regimens. Based on AZA's theoretical ability to suppress NF-κB mediated neuroinflammation, we assign it a Mechanisms grade of "C" (Table 1).

Pre-clinical models

AZA has not been tested in any recognized pre-clinical models of ALS. Therefore, ALSUntangled assigns a "Pre-Clinical" grade of "U"

Cases

In the online community PatientsLikeMe, one PALS reported taking AZA, but provided no further information about clinical outcome (14). One ALSUntangled team member (G.L.) had 3 PALS take AZA while under his care. No effect on their disease progression was appreciable.

Two patients with validated "ALS Reversals" were taking AZA during their recovery (15). One of these patients had preexisting myasthenia gravis and was being treated with AZA, immune globulin, corticosteroids and pyridostigmine for 2 years prior to ALS diagnosis (16). The ALS diagnosis was distinguished from his myasthenia gravis by the presence of both lower and upper motor neuron signs on exam, and by the EMG which showed widespread denervation and reinnervation. He had progressed to severe dysarthria

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Table 1.. Table of evidence for AZA.

	Grade	Explanation
Mechanism	C	AZA can decrease NF-κB expression in a mouse model of ulcerative colitis; theoretically this same effect might allow it to slow ALS progression
Pre-Clinical	U	We found no studies of AZA in recognized pre-clinical models of ALS
Cases	A	Two validated "ALS" reversals in a peer reviewed publication were taking AZA during their recovery
Trials	F	Two small trials in PALS showed no benefit from taking AZA
Risks	D	More than 0 but less than 5% of all exposed patients experience serious adverse events; we caution that very little information is available on PALS treated with AZA

(unintelligible) and confinement to a wheelchair. One month after starting experimental stem cell treatments, his dysarthria improved to where he was able to deliver an intelligible speech to an audience, and he regained the ability to walk. As for the second patient, eighteen months into the symptoms of "clinically definite" limb onset ALS, he started taking a cocktail of medications and supplements eventually including AZA, dexamethasone, testosterone, insulin, omeprazole, ubiquinol, vitamins A, B, C, D and E, calcium, magnesium, licorice, curcumin, CBD oil, glutathione, resveratrol and niagen (17). Over the next few months, his dysarthria and stair climbing improved and his ALSFRS-R score increased from 22 to 26. As we have previously pointed out there can be many possible explanations for ALS reversals like these (15). Based on the two ALS reversals whose cases are published in peer reviewed journals (15,16), we assign a "Cases" grade of "A" (Table 1).

Trials

There have been two published trials of PALS involving AZA. The first trial was a study of five patients with motor neuron disease treated with 2mg/kg/day of AZA for three weeks preceding initiation of partial plasma exchange (18). Limb strength was measured over follow up periods ranging from 6.2 to 13 months and compared to matched historical controls. There was no difference in rate of deterioration between the intervention and control groups. Twenty-one PALS in a second study were treated with prednisolone and AZA (2mg/kg per day) for one year (19). Six patients withdrew from the trial because of side effects or personal choice. No difference in survival was seen between those given the immunosuppressive treatment and matched historical controls. Based on these two small trials, ALSUntangled assigns a "Trials" grade of "F" (Table 1).

Risks, dosing, costs

There is very little data on PALS being exposed to AZA, however, this drug is known to have significant toxicities in clinical use. AZA is considered a group 1 carcinogen by the International Agency for Research on Cancer (20). AZA carries a black box warning for increased risk of malignancy, the most common of which are lymphoma and skin cancer (2). Hematologic toxicity, including myelosuppression (low white blood cell count), thrombocytopenia (low platelet count), anemia (low red blood cell count), and pancytopenia (low counts of white blood cells, platelets and red blood cells) may occur (3). Liver toxicity, manifesting as abnormal liver function tests, may occur (3). Additionally, as an immunosuppressant, AZA confers an increased susceptibility to infection. Progressive multifocal leukoencephalopathy, an often fatal condition caused by JC virus, has been reported in the setting of AZA use (3). To monitor for toxicities, all patients on AZA require close follow up with blood work including a complete blood count with differential and platelets, weekly during the first month, twice monthly for the second and third month and then monthly (3). In addition, liver function and kidney function (creatinine clearance) should be monitored every three months (3). Prior to dosing the drug, genotyping for thiopurine methyl transferase (TPMT) and Nudix hydrolase 15 (NUDT15) should be performed as these can help stratify risk for toxicity and manage dosing (21). In light of AZA's many potentially serious side effects, ALSUntangled assigns a "Risks" grade of "D" (Table 1).

Beyond these documented side effects, AZA could possibly increase the risk of developing ALS. Some believe ALS is caused by acquired nucleic acid changes or variants thereof (22). This process is akin to carcinogenesis, but taking place in a non-dividing cell. If this theory is correct, AZA's mechanism of action would increase the risk of ALS by adversely affecting the DNA of motor neurons. While we have not seen a study looking at the risk of ALS in people taking AZA, it is interesting that one of the "ALS reversals" described above developed ALS after 2 years on this medication.

AZA is most commonly administered orally, but can also be given intravenously (2). The standard target dose for oral administration is 2 mg/kg/day, assuming normal TPMT and NUDT15 activity (23).

The cost of AZA varies based on dose, brand and administration. A standard oral 2mg/kg per

day dose would cost between $180 and $810 per month (retail) (3).

Conclusion

As an immunosuppressant drug, AZA has a plausible mechanism for slowing the progression of ALS. However, there is no pre-clinical data to support its use and two clinical trials did not support efficacy. There are 2 published cases in which ALS reversals occurred on AZA, but it is not clear to us that the AZA actually contributed to the ALS improvements. One of these patients also had myasthenia gravis, which is known to cause reversible weakness and therefore complicates the measurement of ALS. The other patient was taking many different medications and supplements along with AZA. AZA has very serious, potentially fatal, both short and long-term risks associated with its use and requires medical monitoring. Based on the available data, we do not advise the use of AZA as an ALS treatment.

Declaration of interest

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