Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Leflunomide & Teriflunomide

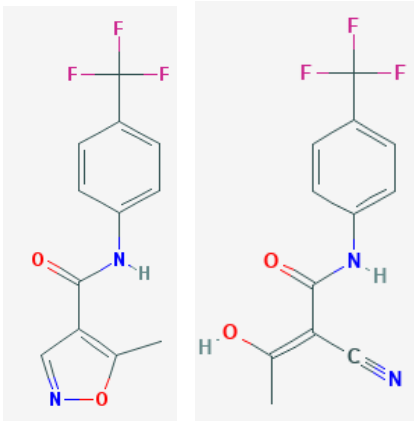
Evidence Summary

Outside of preventing inflammatory damage in autoimmune conditions and possibly augmenting cancer therapies, these drugs are unlikely to benefit the brain or prevent aging related diseases.

Neuroprotective Benefit: Can protect against damage induced by inflammatory lymphocytes, but has poor BBB penetrance and there is no evidence of direct neuroprotective benefit. Side effect of peripheral neuropathy is cause for concern.

Aging and related health concerns: May be useful in cancer treatment in combination therapy, but not useful for prevention. Has the potential to cause hypertension.

Safety: Generally well tolerated, but has black box warning for liver damage. Common side effects are gastrointestinal problems, reversible hair loss, and mild infections.

Availability: Rx	**Dose**: Oral tablet. Leflunomide: 100 mg/day for 3 days loading dose then 20 mg/day maintenance dose for RA. Teriflunomide: 7mg/day or 14 mg/day for MS.	**Chemical formula:** $C_{12}H_9F_3N_2O_2$ **MW**: 270.211 g/mol  Leflunomide Teriflunomide Source: Pubchem
Half-life: ~ 2 weeks	**BBB**: weakly penetrant	
Clinical trials: Phase 1-4 RCTs primarily for RA (33) for leflunomide and MS (5) for teriflunomide. Phase 1 trials for children (n=27) and adults (n=26) with solid tumors, and Phase 2 for prostate (n=44) and ovarian (n=30) cancer showed possible minor benefits. Results from Phase 3 cancer trials not published, additional cancer trials ongoing.	**Observational studies**: Large and small real-world cohorts and retrospective database analyses of RA patients revealed possible increased risk for hypertension with leflunomide use. FDA database analysis with MS patients revealed possible increased risk for liver injury with teriflunomide use.	

What is it? Leflunomide and teriflunomide are immunomodulatory drugs. Teriflunomide is the active metabolite (A7717726) of leflunomide *in vivo*. Approximately 70% of leflunomide is rapidly converted to teriflunomide following oral administration [1]. Teriflunomide is an inhibitor of the mitochondrial enzyme, dihydroorotate dehydrogenase (DHODH), which is important for *de novo* pyrimidine synthesis, and thus can inhibit proliferation in rapidly dividing cells.

Leflunomide, marketed under the trade name Arava® by Sanofi, was FDA approved for use in rheumatoid arthritis (RA) in 1998. In the early 2000s, it was also tested in clinical trials for various types of cancer, but those results were not published, and it was not further developed for that purpose. Recently, there has been renewed interest in its use for chemoprevention. Teriflunomide, marketed

under the trade name Aubagio® by Sanofi, was FDA approved for relapsing-remitting multiple sclerosis (RRMS) in 2012.

Neuroprotective Benefit: Can protect against damage induced by inflammatory lymphocytes, but has poor BBB penetrance and there is no evidence of direct neuroprotective benefit. Side effect of peripheral neuropathy is cause for concern.

Types of evidence:

- 2 clinical trials (Phase 3 RCTs for MS examining brain atrophy-teriflunomide)
- 2 observational studies (Anti-rheumatic drugs in RA patients and dementia risk)
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Autoimmune diseases have been associated with an increased risk for dementia. A retrospective record linked cohort study in the UK found that having a hospital admission for any of 18 autoimmune diseases, including RA and MS, increased the risk of having a subsequent hospital admission for dementia (Risk ratio (RR): 1.20, 95% Confidence Interval (CI) 1.19-1.21) [2]. Similarly, a long-term population-based study in Scandinavia, found that having RA in midlife, increased the odds of having cognitive impairment two decades later (Odds ratio (OR): 2.77, 95% CI 1.26-6.10) [3]. The increased risk for dementia is hypothesized to be related to increased systemic inflammation, in which case controlling the inflammation would be expected to mitigate the risk. Indeed, several studies have found that treatment with anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs), is associated with reduced dementia risk in RA patients [4; 5]. However, **for most of these anti-rheumatics, there is no evidence that people without inflammatory diseases would derive a similar benefit**.

Dementia risk: Potential harm/unclear (leflunomide)

Leflunomide is classified as a conventional DMARD. A recent observational study using the UK Clinical Practice Research Datalink (CPRD) database found that use of conventional DMARDs was associated with decreased risk for dementia in RA patients, however, this study did not include leflunomide, and the results were driven primarily by methotrexate [5]. Meanwhile, a case-control study using the National Health Insurance Research Database in Taiwan found use of conventional DMARDs to be

associated with a 1.63-fold increased risk for dementia, and a significant association with the development of vascular dementia (OR: 1.78, 95% CI 1.21–2.61), but not for Alzheimer's disease (AD) [6]. This study included leflunomide and found that its use for <240 days was associated with the highest risk of all the examined cDMARDs (OR: 2.93, 95% CI = 1.67–5.75), but the risk for use >240 days was not as high (OR:1.30, 95% CI 0.77- 2.20). The higher risk with short-term leflunomide use may be an artifact, in that these patients may have had aggressive RA and were unresponsive to leflunomide. Similarly, the overall increased risk could be due to inadequate RA disease management by leflunomide or conventional DMARDs in general, relative to other drugs for RA. Whether leflunomide is cognitively beneficial or harmful to people without RA is unknown.

Neuroprotection: Potential benefit for MS (teriflunomide)

Teriflunomide has been tested in RCTs for its ability to slow brain atrophy in MS patients. Brain atrophy is the most commonly used measure of neurodegeneration in MS studies. In the Phase 3 TEMSO trial (NCT00134563), **teriflunomide use was associated with less brain volume loss** (BVL) from baseline to year 2 compared to placebo (BVL: 1.29% placebo, BVL: 0.90% Teriflunomide = 30.6% reduction, p=0.0001) as evaluated by SIENA (Structural Image Evaluation using Normalization of Atrophy) [7]. In the Phase 3 TOPIC (NCT00622700) trial, teriflunomide (14mg) also reduced brain atrophy as measured by SIENA, in patients showing first clinical signs of MS by 87%, 29%, and 36% relative to placebo, at 6, 12, and 18 months, respectively [8]. This suggests that teriflunomide, can prevent/slow MS associated neurodegeneration when taken early in the disease course. However, the underlying etiology of neurodegeneration in MS is not well understood, and may be different from the biological mechanisms underlying AD and other dementias. Since teriflunomide is only marginally blood brain barrier (BBB) penetrant, **its beneficial effects are likely related to a reduction in systemic inflammation, and it is unlikely to have any direct effects on neuronal or cognitive function.**

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Animal studies in models of autoimmune diseases have indicated leflunomide and teriflunomide can provide neuroprotection when neuronal damage is caused by pro-inflammatory lymphocytes. Leflunomide was able to reduce clinical symptoms in a rat model (EAN) of autoimmune neuropathy by reducing neuritogenic T cells [9], and teriflunomide attenuated neurodegeneration in a mouse model of a lysosomal storage disease (CLN1) by reducing pathogenic CD8+ T cells [10]. However, **there is no evidence for direct neuroprotection, and peripheral neuropathy is a known side effect of leflunomide, suggesting it could potentially be damaging to axons.**

APOE4 interactions: Unknown

Aging and related health concerns: May be useful in cancer treatment in combination therapy, but not useful for prevention. Has the potential to cause hypertension.

Types of evidence:

- 4 clinical trials (2 Phase 1 and 2 Phase 2 for leflunomide in cancer patients)
- 6 observational studies (for cardiovascular risk in RA patients)
- Numerous laboratory studies

Cancer: Potential benefit for treatment, but not prevention

Treatment

Leflunomide showed evidence of minor benefits in the treatment of several types of cancer in Phase 1 and Phase 2 trials, but the results from subsequent Phase 2 and 3 trials were never made public. In a Phase I trial for 27 pediatric patients (NCT00001573) with refractory advanced solid tumors, one rapidly progressing patient had disease stabilization, but there were no partial or complete responses [11]. In a Phase 2 trial for men with PSA positive prostate cancer, 3/39 patients had >50% decline in PSA levels from baseline, 1/19 patients had an improvement in measurable disease (based on scan), and 3/19 had disease stabilization. For patients with metastatic disease, 4/28 had improvement and 14/28 had stabilization [12]. In a Phase 2 trial for ovarian cancer (n=30), there was one reported partial response lasting 22 months [13]. A Phase 2 trial for Anaplastic Astrocytoma (NCT00003775) was completed in May 2006, a Phase 2/3 trial for Stage 4 Prostate cancer (NCT00004071) was completed in September 2007, and a Phase 3 trial for Glioblastoma multiform (NCT00003293) was completed in May 2001. There is no information about the results from these trials, suggesting leflunomide was found to be less effective than available treatment options. However, leflunomide is currently being tested in a Phase 1/2 trial for refractory Multiple Myeloma (NCT02509052), and will be tested in a Phase 1/2 trial for triple negative metastatic breast cancer (NCT03709446).

Combination Treatment

There has been renewed interest in the potential of leflunomide for cancer treatment in the past few years as an adjunct therapy. Leflunomide has been shown to reduce tumor cell viability and proliferation in a variety of tumor cell lines and mouse xenograft models alone [14; 15; 16], and when used in

combination with chemotherapeutics [13; 17; 18]. It also has anti-angiogenic properties [19]. Chemotherapy induces an increase in pyrimidine levels, which can facilitate chemoresistance [17]. Leflunomide/teriflunomide's action as a *de novo* pyrimidine synthesis inhibitor, could then potentially prevent chemoresistance. In most of these combination studies, **leflunomide had little or no effect on tumor growth when used as a monotherapy**. Leflunomide with 5-fluorocuracil and cisplatin reduced xenograft tumor growth by 74% in a glioblastoma model, 75% for a lung cancer model, and 69% (P=0.0004) in a head and neck cancer model [13]. Leflunomide in combination with doxorubin could induce tumor regression in a triple negative breast cancer model [17], and in combination with the MEK inhibitor selumetinib, reduced tumor growth in a melanoma model [18]. However, a Phase 1 trial for leflunomide in combination with the BRAF inhibitor vemurafenib for V600 mutant metastatic melanoma (NCT01611675), was recently terminated due to adverse events. **A combination therapy that is safe and effective in humans has not yet been found.**

Prevention

While clinical trials for leflunomide and teriflunomide did not show evidence for an increased incidence of malignancies [20; 21], there have been various case reports of patients treated with these therapies developing cancer, especially lymphoma [22]. **This suggests that leflunomide/teriflunomide are not likely to be effective in the prevention of cancer.**

Diabetes: Potential benefit for RA patients with diabetes

Leflunomide may be most beneficial for patients with RA and Type 2 diabetes, as patients taking leflunomide were found to have significantly lower plasma glucose levels, compared to those taking other DMARDs (83.6±13.4 mg/dL vs. 93.0 ±19.2, adjusted P=0.006), and marginally lower body mass index (BMI) (27.5±6.3 vs. 29.5±6.8 kg/m^2, adjusted P=0.07) in an observational cross-sectional study in the USA [23]. However, the study found no significant difference in blood pressure, HDL, LDL, triglycerides, homocysteine, or F2-isoprostanes in leflunomide users compared to non-users.

Leflunomide was also demonstrated to normalize blood glucose levels and overcome insulin resistance in mouse models of diabetes (ob/ob and high-fat diet) [24]. Cell culture studies suggest that this effect stems from modulation of the mTOR pathway. Teriflunomide is an inhibitor of the serine/threonine kinase S6K1, which is downstream of mTOR. S6K1 phosphorylates insulin receptor substrate-1 (IRS-1) and desensitizes insulin receptor signaling. However, leflunomide's ability to modulate this pathway is rather weak, making it far less effective than currently available anti-diabetics.

Cardiovascular Disease: Potential harm/unclear

People with RA have a high prevalence of hypertension, which puts them at greater risk for cardiovascular disease. A questionnaire based cross-sectional review of RA patients from 48 countries (n= 4363) found that the prevalence for lifetime cardiovascular events was 9.3%. The prevalence for risk factors was 32% for hypertension, 14% for hyperlipidemia, 8% for diabetes, 43% for ever-smoking, 73% for physical inactivity, and 18% for obesity [25]. This study found that exposure to DMARDs reduced cardiovascular disease morbidity, and leflunomide had a hazard ratio (HR) of 0.59 (95% CI 0.43 to 0.79). However, other studies have indicated that RA patients with leflunomide have an increased risk for cardiovascular disease and its risk factors, relative to patients treated with other DMARDs.

Atherosclerosis:

Usage of leflunomide was correlated with the abnormal small artery compliance, which contributes to atherosclerosis, in RA patients OR:6.170 (95%CI 1.510- 25.215) in a small (n=185) real-world observational study in China [26].

Hypertension:

On Drugs.com, both leflunomide and teriflunomide have a moderate potential hazard warning for individuals with hypertension. In a prospective case-control study in Pakistan (n=44), patients receiving leflunomide increased their systolic blood pressure from 108.5 and 135.4mmHg, and 41% developed hypertension following 1 year of use [27]. In an observational review of medical records in Greek RA patients (n=325), hypertension was associated with leflunomide use (HR per 1 year of treatment : 1.02, 95% CI 1.00–1.05) [28], and in a review of the Veteran's Affairs database (n=21, 216) **RA patients treated with leflunomide had increased blood pressure and a greater risk of incident hypertension** compared with patients treated with methotrexate (HR: 1.53, 95% CI 1.21–1.91; P < 0.001) [29]. There are also several case reports of patients developing pulmonary arterial hypertension following leflunomide treatment, which led to a warning by the EMA [30]. However, it is possible that these results are influenced by patient selection bias, such that RA patients who receive leflunomide treatment may have already been at higher risk due to underlying conditions in which other available DMARDs were contraindicated, and/or had more aggressive disease that was inadequately controlled by first line treatment options.

Overall, the evidence suggests that leflunomide offers less cardiovascular benefits in RA patients, as it may induce hypertension, compared to other available DMARDs, and appears unlikely to offer any cardiovascular benefit to those without underlying inflammatory autoimmune conditions.

Safety: Generally well tolerated, but has black box warning for liver damage. Common side effects are gastrointestinal problems, reversible hair loss, and mild infections.

Types of evidence:

- 2 systematic reviews (Cochrane reviews for leflunomide in RA patients based on 33 RCTs, and teriflunomide in MS patients based on 5 RCTs)
- 4 clinical trials (Phase 3 extension and Phase 4 for teriflunomide in MS patients, 2 Phase 1 trials for patients with advanced solid tumors for leflunomide)
- 4 observational studies (3 database/cohort studies of RA patients for leflunomide, 1 database analysis of MS patients for teriflunomide)
- Numerous laboratory studies

Based on Cochrane systematic reviews of clinical trials for leflunomide in RA and teriflunomide in MS, the **primary adverse event of concern is elevated liver function tests** (alanine aminotransferase levels) [20; 21]. Both drugs contain FDA black box warning labels for **hepatotoxicity** on their package inserts, and recommendations that alanine aminotransferase levels be checked 6 months prior to and 6 months after starting the drug. If levels of this liver enzyme exceed 3X the upper limit of normal, the drug is to be discontinued. Real-world observational studies have found that severe liver injury is rare. In RA patients starting leflunomide treatment (n=101), grade 2/3 liver test elevations were found in 8.9% of patients, but they typically occurred within the first 6 months, and then resolved upon follow-up, with no serious hepatotoxicity [31]. An analysis of the FDA adverse events reporting system (FAERS) (11, 764 cases of liver injury out of 8,862,213 cases collected) examining liver injury in MS patients, found that liver injuries were a common feature of MS drugs and that the risk odds ratio for teriflunomide was ROR: 2.31 (95% CI, 2.12–2.52) for overall liver injury, but it was not associated with increased risk for serious liver injury [32].

Adverse events for leflunomide

In 33 clinical trials for leflunomide, the most common other adverse events were **gastrointestinal symptoms** (RR: 1.60, 95% CI 1.28 to 1.99) and **reversible hair loss** (alopecia) (RR: 6.60, 95% CI 2.36 to 18.44) [20]. Hypertension was not significantly different from placebo, but was higher than for methotrexate users. A real-world retrospective analysis of the RAPPORT database (n=1671) found that adverse events (AE) were reported by 29% of users [33]. Nuisance AE (31% of patients with AE) and diarrhea (29%) were the most common, followed by infection (19%), and liver dysfunction (13%). 68% of reported AE were moderate, 16% severe, and 25% persisted. Leflunomide was discontinued due to intolerance by 32% of prevalent users. The RABBIT prospective cohort study in Germany (n=5,126)

found an increased incidence of pancreatic cancer in leflunomide treated RA patients (Standardized incidence rate (SIR): 3.10, 95% 1.25-6.45) vs patients not exposed to leflunomide (SIR: 0, 95% CI 0-4.32), however, there was no increased incidence found in the corresponding British (n=16,930) and Swedish (n=19,351) cohorts [34]. In Phase 1 trials in cancer patients, neurotoxicity developed at infused doses of 440 mg/m^2/day in pediatric patients [11], and grade 3 neutropenia developed in adults [35]. Most common AE were gastrointestinal-related events.

FDA warnings: Hepatotoxicity, use in pregnant women, risk of infection/immunosuppression, peripheral neuropathy, skin reactions, and malignancy (no evidence for increased risk, but possible).

Adverse events for teriflunomide

In 5 clinical trials for teriflunomide (n=3,231), the most common adverse events associated with teriflunomide were **diarrhea, nausea, reversible hair thinning** (alopecia**), elevated alanine aminotransferase, neutropenia and lymphopenia** [21]. A 9-year long term extension (NCT00803049) (n=742) of the Phase 3 TEMSO trial, found that 11% discontinued due to AE, primarily due to elevated liver enzyme levels, and 20% of patients experienced a serious AE [36]. Other AE were reversible hair thinning, neutropenia/leukopenia, and hypertension. There were 3 cases of peripheral neuropathy potentially related to treatment. Infections were typically mild, and opportunistic infections were rare. In the global Phase 4 open-label Teri-PRO study (NCT01895335), patients who switched to teriflunomide from other MS therapies (n=594), experienced AE (hair thinning, elevated liver tests, diarrhea) similar to those in RCTs [37].

FDA warnings: Hepatotoxicity, use in pregnant women, risk of infection/immunosuppression, peripheral neuropathy, acute renal failure, hyperkalemia, skin reactions, increase in blood pressure, and interstitial lung disease worsening.

Leflunomide has demonstrated anti-viral activity against cytomegalovirus (CMV), BK virus, Epstein-Barr virus (EBV), and herpes simplex virus (HSV), which makes it an effective immunosuppressant agent for organ transplants with risk for viral reactivation [38; 39]. However, similar to other immunosuppressants, serious infections [40] have occurred in some patients treated with leflunomide or teriflunomide, including the fatal opportunistic infection associated disease, progressive multifocal leukoencephalopathy [41; 42]. Older patients are at the greatest risk for infection [43].

Leflunomide and teriflunomide are also contraindicated during pregnancy due to potential risk for teratogenicity, as indicated by an FDA black box warning. There is an active observational study examining the potential risk for birth defects or adverse pregnancy outcomes in teriflunomide exposed

pregnancies (NCT03198351). Another study is examining whether teriflunomide can be transmitted from men to their female partners during sexual intercourse (NCT02679885).

Drug interactions:

According to Drugs.com, there are 763 drugs known to interact with leflunomide, and 867 with teriflunomide. The list is primarily comprised of other immunosuppressant/anti-inflammatory drugs. There is a major interaction with alcohol use, and moderate interaction with caffeine.

Sources and dosing:

Leflunomide and teriflunomide are both available by prescription as oral tablets, and are marketed through Sanofi, as Arava® and Aubagio®, respectively. An authorized generic version of leflunomide was made available in 2015. Leflunomide has a loading dose of 100 mg for three days, followed by a maintenance dose of 20 mg/day. For tolerability reasons, the dose can be lowered to 10 mg/day. Teriflunomide is dosed at 7 mg or 14 mg (more common) per day. Due to the long half-life, these drugs may remain in the body for several weeks after discontinuation.

Research underway:

There are currently 8 active trials and 12 recruiting trials for teriflunomide, according to Clinicaltrials.gov. Nearly all the trials relate to its use in MS patients.

There are currently 2 active trials, 15 recruiting, and 3 not yet recruiting trials for leflunomide, according to Clinicatrials.gov. Most of the trials are for use in patients with rheumatic diseases. It is also being tested for cancer, and kidney transplant patients with a risk for BK virus reactivation (NCT01620268).

Cancer trials include: A Phase 1/2 trial for previously treated triple negative breast cancer (NCT03709446), with an estimated completion date of October 2021; a Phase 1/2 trial for refractory multiple myeloma (NCT02509052), with an estimated completion date of June 2019.

Search terms:

Pubmed, Google: Leflunomide +

aging, neurodegeneration, neuroprotection, dementia, Alzheimer's diseaes, cardiovascular, hypertension, cancer, diabetes, liver, infection, safety, meta-analysis, systematic review, real-world, anti-viral, pml, neuropathy

Teriflunomide +

aging, neurodegeneration, neuroprotection, dementia, Alzheimer's disease, brain atrophy, cardiovascular, cancer, liver, infection, safety, meta-analysis, systematic review, real-world, neuropathy, lymphoma

Websites visited for Leflunomide:

- Clinicaltrials.gov
- Treato.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Patientslikeme.com

Websites visited for Teriflunomide:

- Clinicaltrials.gov
- Treato.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Patientslikeme.com
- Cafepharma

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