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.

Lenalidomide

Evidence Summary

Although lenalidomide has anti-inflammatory effects, the extent of blood-brain-barrier penetrance is unknown; safety concerns include hematological toxicity, thromboembolism, infections, and cancers.

Neuroprotective Benefit: Although lenalidomide has anti-inflammatory effects, a case report in multiple myeloma patients reported significant cognitive decline with lenalidomide treatment. Consistency of blood-brain-barrier penetrance is not established.

Aging and related health concerns: Risk for cancer, cardiovascular disease, and neuropathy have been observed, though all clinical data come from cancer patients.

Safety: Lenalidomide treatment is associated with increased risks for hematological toxicity, venous and arterial thromboembolism, infections, and cancers.

What is it? Lenalidomide (Revlimid®) was first approved in 2006 for use with dexamethasone in patients with multiple myeloma who received at least one prior therapy. Since then, it has been approved for myelodysplastic syndromes and mantle cell lymphoma. In February 2017, lenalidomide monotherapy was approved in the US for maintenance treatment after autologous stem cell transplantation in patients with newly diagnosed multiple myeloma (Syed, 2017). Lenalidomide inhibits TNF-α production, stimulates T cells, and has immunomodulatory and anti-neoplastic effects. It also reduces levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and inhibits angiogenesis (NCI Thesaurus). It is a thalidomide analogue with improved potency and reduced toxicity compared to thalidomide.

Neuroprotective Benefit: Although lenalidomide has anti-inflammatory effects, a case report in multiple myeloma patients reported significant cognitive decline with lenalidomide treatment. Consistency of blood-brain-barrier penetrance is not established.

Types of evidence:

- 4 case reports of cancer patients receiving lenalidomide
- 1 non-human primate study examining blood-brain-barrier penetrance of lenalidomide
- 1 review

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

One case report of 2 male patients with multiple myeloma reported significant cognitive impairment associated with lenalidomide treatment (Rollin-Sillaire et al., 2013). In both cases, neuropsychological manifestations appeared within 1 month of lenalidomide initiation. Upon withdrawal of the drug, one patient recovered normal cognitive function and independence in activities of daily living, whereas mild cognitive impairment persisted in the other patient. Of different cognitive functions tested, lenalidomide negatively impacted episodic memory the most. In one of the patients, SPECT imaging revealed hypoperfusion in the left temporal lobe.

Lenalidomide's putative neurotoxicity is likely influenced by specific risk factors including previous chemotherapy, prior mild cognitive impairment, age, and the presence of cerebrovascular lesions. Several potential mechanisms were discussed in the case report, including direct neurotoxic effect of the drug, oxidative stress and DNA damage, induced hormonal changes, immune dysregulation, cytokine release, vascular injury, blood clotting in small vessels, and a genetic predisposition.

Human research to suggest benefits to patients with dementia: Unavailable.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
There are no published reports, preclinical or clinical, that have demonstrated improvement in cognitive functions with lenalidomide.

The extent of blood-brain-barrier (BBB) penetrance of lenalidomide in humans is still unclear. However, lenalidomide may readily cross a damaged BBB (Rollin-Sillaire et al., 2013). A case study of a 74-year-old man with B-cell lymphoma involving the CNS reported that while the patient failed chemotherapy, he was able to achieve remission on lenalidomide therapy (25 mg/day for 21-day cycle combined with 20 mg of weekly dexamethasone) (Cox et al., 2011). In this patient, lenalidomide was detected in the cerebral spinal fluid (CSF). Two other case studies also reported that lenalidomide led to improvement in patients with CNS relapse of diffuse large B-cell lymphoma (Rubenstein et al., 2011; Cencini et al., 2017). The two patients were 59- and 83-years old. A study in rhesus monkeys showed that 2 out of 3 monkeys showed detectable levels of lenalidomide in the CSF after oral administration (Muscal et al., 2012). No explanations were provided on why lenalidomide was undetectable in the third monkey.

In human peripheral blood mononuclear cells, lenolidomide inhibits pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and IL-12) and enhances the production of anti-inflammatory cytokine IL-10 (Syed, 2017). If these actions also occur in the brain, then it is expected that lenalidomide will decrease neuroinflammation. It is unclear whether the potential anti-inflammatory and neuroprotective effects suggested by its mechanism of action outweighs lenalidomide's putative neurotoxicity as suggested in the case report on cognitive impairment.

APOE4 interactions: Unknown

Aging and related health concerns: Risk for cancer, cardiovascular disease, and neuropathy have been observed, though all clinical data come from cancer patients.

Types of evidence:

- 3 prospective studies, 2 in multiple myeloma patients and 1 in relapsed chronic lymphocytic leukemia patients
- 2 case studies
- 4 reviews

Cancer: HARM. In a meta-analysis of 1,208 newly diagnosed multiple myeloma patients, the incidence of a second primary malignancy was higher with lenalidomide therapy compared to placebo or observation (McCarthy et al., 2017). Frequencies of hematologic second primary malignancy were 5.3% for lenalidomide-treated patients and 0.8% for those in the placebo/observation group.

Cardiovascular disease: HARM. Several studies have associated lenalidomide with venous thromboembolisms, arterial thromboembolisms, myocardial infarction, and cerebrovascular events. A review of various myeloma therapies suggested that lenalidomide is associated with cardiovascular events, especially when used in combination with dexamethasone and/or cytotoxic chemotherapy (Li et al., 2017). For example, venous thromboembolism incidences were 26% for lenalidomide plus high-dose dexamethasone treatment and 12% for lenalidomide plus low-dose dexamethasone. In a long-term follow-up of 704 multiple myeloma patients recruited in 2 large randomized phase III trials, the incidences of myocardial infarction and cerebrovascular events were 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone, compared with 0.57% and 1.7% in patients treated with dexamethasone alone (Gov.UK). In a prospective study of 32 relapsed lymphocyte leukemia patients receiving lenalidomide treatment (10 or 20 mg/day for 21 days on and 21 days off), 5 patients developed 6 incidents of deep venous thrombosis over one year (annual incidence, 16%)(Aue et al., 2011). Three of these incidents were considered lenalidomide-related. Notably, in patients with lenalidomide-related deep venous thrombosis, TNFα and soluble vascular endothelial adhesion molecule 1 (sVCAM1) were more strongly upregulated than all other patients. This is in contrast to lenalidomide's proposed action to inhibit TNFα.

In a case study, an 85-year-old woman with recurrent follicular lymphoma was treated with lenalidomide (10 mg/day) and low-dose dexamethasone (8 mg/week), and within 17 days she developed congestive heart failure, which led to multiorgan failure and death (Carver et al., 2010). Postmortem examination of the heart confirmed the absence of coronary artery disease, and histopathological examination of the myocardium revealed a diffuse lymphocytic/eosinophilic inflammatory infiltrate with associated acute and chronic myocardial injury affecting all 4 chambers of the heart, consistent with myocarditis. The authors concluded that lenalidomide may have been the cause of drug-induced myocarditis in this patient.

Neuropathy: HARM. In a 5-year prospective study of 19 relapsed/refractory multiple myeloma patients on long-term lenalidomide therapy, up to 50% developed (or had worsened) sensory axonal neuropathy (Dalla Torre et al., 2016). Reduced dorsal sural nerve sensory action potential amplitude was the first neurophysiologic change. However, neuropathy was usually mild and independent of the cumulative

dose of lenalidomide. A case study of a patient with multiple myeloma also reported that 7 cycles of lenalidomide treatment resulted in exacerbation of existing peripheral neuropathy, with mild numbness and transient decrease in the Functional Assessment of Cancer Therapy scale/Gyenocologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) score (Kamimura et al., 2014). Comparative effectiveness research assessed the effectiveness and safety of lenalidomide versus thalidomide in a population-based cohort including 1,264 multiple myeloma patients (Luo et al., 2017). This study reported that compared with thalidomide treatment, lenalidomide was associated with a reduced risk of peripheral neuropathy (HR=0.71, 95% CI, 0.56-0.92). Thus lenalidomide has less neurotoxic effects compared to thalidomide.

Infection: HARM. A meta-analysis of 11 phase II/III clinical trials totaling 3,210 multiple myeloma patients reported that lenalidomide treatment is associated with a significantly increased risk of high-grade infection, with an overall incidence of 14.32% (95% CI: 12.08%-16.90%) and pooled RR of 2.23 (95% CI: 1.71-2.91)(Ying et al., 2017). An older meta-analysis also reported a significantly higher odds ratio for infection with lenalidomide treatment (OR = 2.82, 95% CI = 1.67 to 4.73) compared to placebo in multiple myeloma patients (Gao et al., 2014). The mechanisms by which lenalidomide increases the risk of infection in multiple myeloma patients remain unclear. It is unknown whether similar infection risks are expected for people without multiple myeloma.

Safety: Lenalidomide treatment is associated with increased risks for hematological toxicity, venous and arterial thromboembolism, infections, and cancers.

Types of evidence:

- 9 meta-analyses or systematic reviews
- 1 review

In the US, lenolidomide carries a boxed warning regarding potential emryo-fetal toxicity, hematological toxicity (neutropenia and thrombocytopenia), and venous and arterial thromboembolism (Revlimid® Safety Information). Lenolidomide can cause serious side effects including increased risk of death in people who have chronic lymphocytic leukemia—these risks include serious heart problems that can lead to death, including atrial fibrillation, heart attack, or heart failure. Also, an increase in new (second) cancers have occurred in patients who received lenolidamide and a hematopoietic stem cell transplant, including certain blood cancers, skin cancers, and others (discussed above).

The most common side effects of lenolidamide include diarrhea, rash, nausea/vomiting, constipation, tiredness, fever, itching, swelling of limbs and skin, trouble sleeping, dizziness, and coughing (WebMD.com).

Clinical data: Multiple meta-analyses have examined the adverse effects associated with lenalidomide treatment in cancer patients (Aquiar et al., 2017; Ying et al., 2017 ; Wang et al., 2016; Lian et al., 2016; Qiao et al., 2015; Gao et al., 2014; Palumbo et al., 2014).

A meta-analysis of 17 randomized controlled trials including a total of 6,742 multiple myeloma patients reported that lenalidomide-based regimens were associated with significantly increased frequencies of neutropenia (RR=2.58; 95% CI, 1.58--4.24), thrombocytopenia (RR=2.91; 95% CI, 1.97–4.28), grades 3-4 anemia (RR=1.68; 95% CI 1.09–2.57), and grades 3-4 thrombosis or embolism (RR=3.43; 95% CI, 1.43–8.25) (Wang et al., 2016).

In a meta-analysis of 17 cohort studies including 2,160 patients with myelodysplastic syndromes (a group of cancers in which production of healthy blood cells is impaired) receiving lenalidomide treatment, the incidences of grades 3-4 neutropenia, thrombocytopenia, leukopenia, anemia, deep vein thrombosis, diarrhea, fatigue and rash were 51% (95% CI, 30-73%), 31% (95% CI, 20-42%), 9% (95% CI, 5-13%), 7% (95% CI, 2-12%), 3% (95% CI, 2-5%), 3% (95% CI, 1-5%), 2% (95% CI, 1-4%) and 2% (95% CI, 1-3%), respectively (Lian et al., 2016).

As discussed in the Aging section above, meta-analyses have reported that lenalidomide treatment is also associated with significantly increased risks of high-grade infection (RR=2.23; 95% CI: 1.71-2.91)(Ying et al., 2017) and a second primary malignancy (McCarthy et al., 2017).

Elderly/frailty: While elderly patients (over 75 years old) with multiple myeloma benefited from lenalidomide/dexamethasone treatment, the benefit was less pronounced than in patients under 75 years old (Zweegman et al., 2017). Lenalidomide may be more toxic and less efficacious in frail patients, leading to lower quality of life.

Drug interactions: A total of 204 drugs are known to interact with lenalidomide, with 94 having major interactions (Drugs.com). Examples include statins (lovastatin, fluvastatin, simvastatin), estrogens (birth control and hormone replacement therapies), immunosuppressants (Talimogene Laherparepvec), and vaccines (measles, mumps, rubella, zoster, etc.),

Sources and dosing: Lenalidomide (Revlimid®) is a prescription medicine manufactured by Celgene. The patent expires in 2019, at which point generic versions will likely be commercialized.

In newly diagnosed myeloma patients, the recommended starting dosage is 10 mg/day for 3 months, then the dosage is increased to 15 mg/day if tolerated (Syed, 2017). Dosage reductions are recommended to manage neutropenia, thrombocytopenia or other lenalidomide-related toxicity.

Research underway: Based on ClinicalTrials.gov, there are 369 "active" clinical studies (not yet recruiting, recruiting, enrolling by invitation, and active/not recruiting) testing lenalidomide. These studies are testing lenalidomide for various cancers. No studies are currently examining the effects of lenalidomide for dementia or age-related cognitive decline.

Search terms:
Pubmed, Google: Lenalidomide, Revlimid

- + cognitive, + memory, + Alzheimer's, + ApoE, + blood-brain-barrier, + meta-analysis, + cardiovascular, + diabetes, + neuropathy, + safety

Websites visited for Lenalidomide:

- Clinicaltrials.gov
- Treato.com
- Drugs.com
- WebMD.com
- DrugAge (0)
- Geroprotectors (0)