CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
ACENTRA HEALTH
QUARTERLY NEWSLETTER

Olmesartan-Induced Sprue-Like Enteropathy

Angiotensin II Receptor Blockers (ARBs) are a class of antihypertensive medications that lower blood pressure by inhibiting a portion of the renin-angiotensin-aldosterone system (RAAS). The RAAS is a network of organs and hormones that work together in a feedback loop to maintain blood volume and blood pressure homeostasis. In instances where blood volume or pressure drops, the liver releases angiotensinogen which is ultimately converted to angiotensin II (ATII). ATII then binds to angiotensin$_1$ (AT_1) receptors which compresses the smooth muscle surrounding the vascular system causing vasoconstriction and increasing blood pressure (Image 1[1]).

ARBs work by competitive inhibition, binding to AT_1 receptors and blocking ATII from binding. This results in relaxation of smooth muscle, vasodilation, lower blood pressure, and a downstream reduction in aldosterone which further decreases blood pressure by reducing sodium and water retention via the kidneys (Image 2[2]).[3,4,5]

ARBs are one of five main classes of medications used to treat hypertension (HTN). Other classes include diuretics, beta blockers (β-blockers), calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEI). ARBs (and ACEIs) are interchangeable and can be considered first line treatment for HTN in patients with comorbid heart failure or kidney disease.[6] ARBs are an alternative to ACEIs in patients who are intolerant due to cough or angioedema.[4] ARBs should not be used in women who are pregnant. While ARBs do not carry many side effects, hypotension and hyperkalemia can occur, especially when used in combination with potassium sparing duiretics.[4] There are 7 drugs within the class: losartan was the first to receive FDA approval in 1995 followed by irbesartan (1997), candesartan (1998), telmisartan (1998), valsartan (2002), olmesartan (2002), eprosartan* (2006), and azilasartan (2011).[7] The ARB class has signature nomenclature of generic names that end in "sartan." One noteworthy ARB, and the subject of this newsletter, is olmesartan.

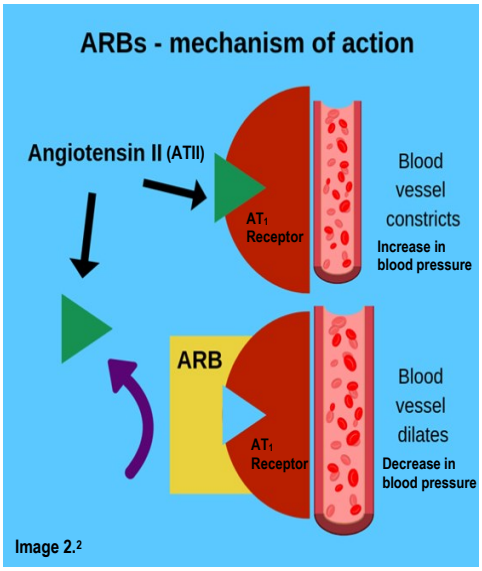

Image 2.[2]

*Eprosartan was discontinued in 2020, due to business reasons.[8]

Olmesartan is the third most used ARB within the Connecticut Medicaid population (Table 1). During the previous one year of claim history, 4,129 unique recipients enrolled in CT Medicaid received a prescription for olmesartan or an olmesartan containing product. Olmesartan can be formulated alone or in combination with other antihypertensives such as hydrochlorothiazide or amlodipine. Olmesartan medoxomil is a prodrug that is converted to the active form olmesartan within the body and is highly selective for AT_1 receptors.[9] Olmesartan is noteworthy due to the risk of a rare but serious side effect of drug induced sprue like enteropathy. Enteropathy is a disease or disorder affecting the intestines and sprue-like

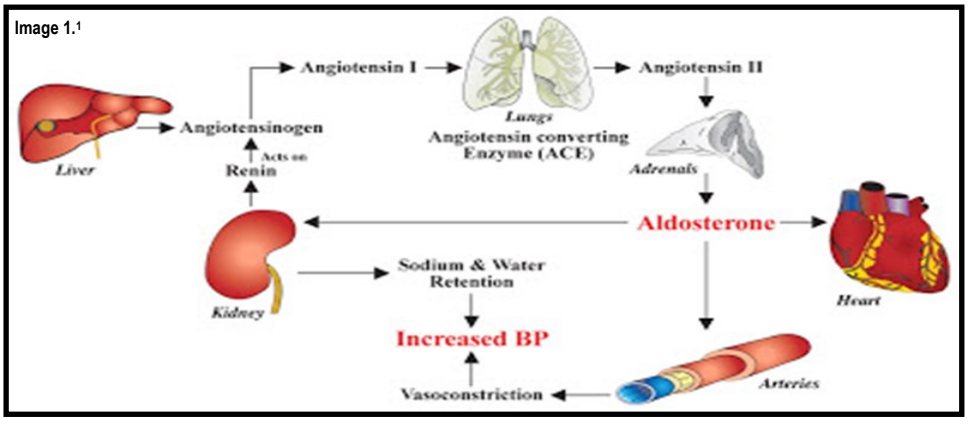

Image 1.[1]

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refers to the histological changes to the intestinal villi, specifically villous atrophy (Image 3).[9,10]

The first article to report olmesartan induced sprue-like enteropathy was published by Rubio-Tapia et al in 2012, highlighting 22 patient cases.[9] The authors documented 6 clinical features that must be present in order to make the association between treatment with olmesartan and the development of sprue-like enteropathy: [9]

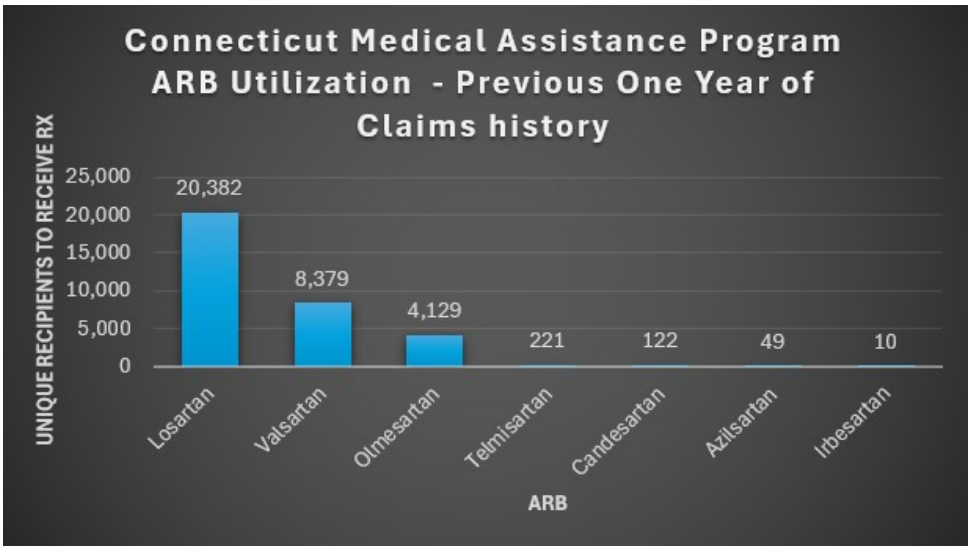
- Chronic diarrhea, weight loss, steatorrhea
- Negative testing for celiac disease (endomysial and tissue transglutaminase antibodies (tTG) IgA antibody)
- Histopathological evidence of villous atrophy (with or without collagen deposition or intraepithelial lymphocytosis)
- Lack of response to gluten-free diet
- Exclusion of other causes of enteropathy
- Evidence of improvement after discontinuation of olmesartan (clinical and histological)

In response to these findings, the Food and Drug Administration (FDA) listed olmesartan under safety surveillance due to reports of diarrhea and malabsorption in October 2012. In July 2013, the FDA released drug safety information regarding sprue-like enteropathy with diarrhea and weight loss, which coincided with package insert changes.[11,12,13]

Other case reports have documented similar findings since the original report by Rubio-Tapia et al.[11,14,15] In 2019, Kamal et al reported on 248 cases of sprue like enteropathy concluding 94% were associated with olmesartan, whereas 6% were associated with other ARBs in the class. The authors concluded that while sprue-like enteropathy may be a class effect, it is partial to olmesartan.[7]

The hallmark presentation of olmesartan induced sprue like enteropathy is non-bloody chronic diarrhea (5-10 times per day) coupled with weight loss. Other symptoms can include flatulence, nausea, and abdominal pain. Chronic diarrhea can result in severe dehydration, electrolyte imbalance, iron deficiency anemia, micronutrient malabsorption, and vitamin deficiency, acute renal failure, or the need for total parenteral nutrition.[9,10,16] It should be noted that olmesartan-induced sprue-like enteropathy is frequently overlooked until patients are hospitalized due to severe dehydration or acute renal failure. Upon hospitalization, olmesartan is generally held due to hypotension or renal impairment, at which point GI symptoms may begin to resolve. Clinicians should be aware that this is an opportune time to recognize this adverse drug event.[10]

Celiac disease is the most common cause of villous atrophy and clinically, nearly identical to olmesartan induced sprue like enteropathy, so it must be ruled out as a differential diagnosis. Celiac disease can be ruled out by a negative antibody test and lack of a response to a gluten free diet.[11] Other disease states such as autoimmune enteropathy, graft versus host disease, common variable immune deficiency, bacterial overgrowth, collagenous sprue, HIV, tropical sprue, giardiasis, Whipple disease, viral disease, and inflammatory bowel disease should also be ruled out when considering olmesartan induced sprue like enteropathy.[7,9,17] Other medications that can cause sprue-like enteropathy such as chemotherapy medications (mycophenolate, azathioprine), methotrexate, interferon alpha, antibiotics, laxatives, magnesium/calcium antacids, colchicine, and NSAIDs should also be considered as a differential diagnosis.[11,18]



While scientists do not know for certain why olmesartan causes drug induced sprue like enteropathy, there are four theories that attempt to explain this phenomenon:[9,17,18]

- Cell-mediated immunity
- Inhibition of transforming growth factor β
- Intestinal cell apoptosis
- Immunological predisposition

Olmesartan induced enteropathy can occur months to years after initiation of

therapy. Due to the lag time between initiation of therapy and development of symptoms, clinicians theorize the reaction occurs by delayed cell-mediated immunity, rather than hypersensitivity to olmesartan itself.[9] The immune reaction is thought to disrupt gastrointestinal (GI) homeostasis and cause damage to the brush border of the small intestine.[17,18] The second theory involves growth factor β, an immunoregulatory cytokine that helps to create balance within the GI tract.[9,17] When olmesartan binds to AT_1 receptors, it inadvertently inhibits the transformation of growth factor β, blocking it's contribution to maintaining GI homeostasis. The third theory pertains to AT_2 receptor induced intestinal cell apoptosis. Olmesartan competes with ATII to selectively bind to AT_1 receptors. When AT_1 receptors become saturated, circulating ATII will then bind to AT_2 receptors which induces intestinal cell death and villous atrophy.[7] The fourth and final theory takes into account immunological predisposition. Scientists know that the presence of the HLA-DQ2/DQ8 genotype predisposes patients to celiac disease. Rubio-Tapia et al reported that while none of their cases tested positive for celiac disease, approximately 70% had the HLA-DQ2/DQ8 genotype and developed olmesartan induced sprue like enteropathy, suggesting that patients may be genetically predisposed to develop this side effect.[17]

Pathological changes and evidence of villous atrophy must be present to confirm diagnosis of olmesartan induced sprue like enteropathy (Image 3).[9] Endoscopy *with* biopsy is crucial for a positive diagnosis because endoscopy alone may not show villous changes.[10] Other histological changes that may be present but are not required for diagnosis include mucosal inflammation, duodenal mucosa atrophy, lymphocyte and plasma cell infiltration, glandular apoptosis, crypt rarefaction, or crypt architectural distortion.[17,18,19]

The most compelling evidence for the causal relationship between olmesartan therapy and the development of enteropathy is symptom resolution upon discontinuation. The gold standard treatment is cessation of therapy and once stopped rechallenge is not recommended due to risk of serious adverse events.[9,19] Clinical recovery is swift, however, villous atrophy and other pathological changes can take months to heal.[19] Medications such as steroids, antidiarrheals, and immunosuppressive medications have been used to treat or control residual symptoms but the mainstay of treatment is discontinuation.

Olmesartan induced sprue like enteropathy is rare, however, it should be considered in patients receiving therapy who present with chronic diarrhea and weight loss. Development isn't always immediate; on average it takes three years after initiation of olmesartan to emerge as a side effect.[9] Recognition is important but can be challenging to diagnose due to the nonspecific nature of the GI symptoms. It is important to take a comprehensive history, including medication history, and to use caution when prescribing olmesartan in patients with underlying autoimmune disorders.

There are many differential diagnoses that resemble olmesartan induced sprue like enteropathy which must be considered and ruled out. Histological changes confirmed by duodenal biopsy are necessary for a positive diagnosis, along with symptom resolution upon discontinuation of therapy. Detection can save lives. The most severe clinical consequences include renal failure and death. Therefore, it is important to stay vigilant and aware of this rare but consequential adverse drug event.

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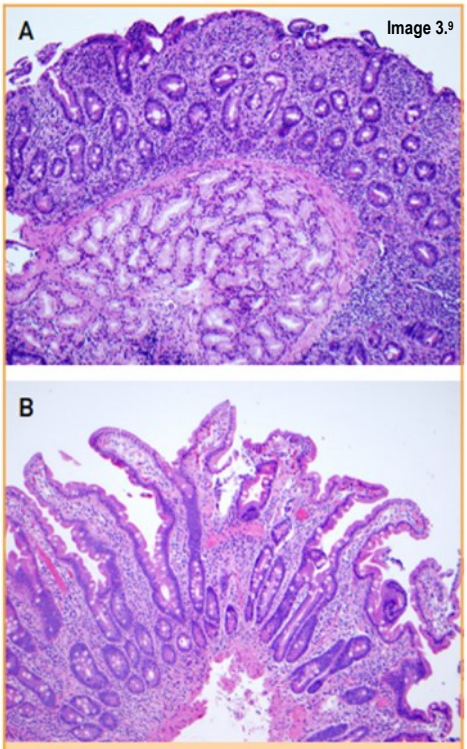

FIGURE. Photomicrographs showing reversible spruelike enteropathy associated with olmesartan (hematoxylin-eosin, original magnification ×100). A, Duodenal biopsy specimen obtained while the patient was taking olmesartan shows total villous atrophy and intraepithelial lymphocytosis. B, Biopsy specimen obtained 6 months after withdrawal of olmesartan and initiation of a gluten-containing diet shows recovery of villi on duodenal mucosa.