Novel Drugs for Geriatric Patients

Geriatrik Hastalarda Kullanılan Yeni İlaçlar

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ABSTRACT While the global population of individuals aged 65 and older is projected to surpass 80 million by 2050, this situation highlights the need for personalized and accessible elderly care. This projection intersects with the demand for advanced treatments that enhance both longevity and quality of life, and prevalent chronic diseases in geriatric patients bring along high-cost treatments. This article addresses novel drugs used in treatment of chronic diseases in geriatric patients, including recently approved medications, lecanemab, aducanumab, edoxaban, and evolocumab.

Keywords: Geriatrics; aducanumab; edoxaban; evolocumab; lecanemab

ÖZET 2050 yılına kadar 65 yaş ve üstü bireylerin küresel nüfusu 80 milyonu aşması öngörülmek ile birlikte bu durum kişiye özel ve erişilebilir yaşlı bakımına olan ihtiyacı vurgulamaktadır. Bu öngörü hem uzun ömür hem de yaşam kalitesini artıran ileri tedavilerin talebiyle kesişmektedir ve geriatrik hastalarda gelişen yaygın kronik hastalıklar yüksek maliyetli tedavilerini beraberinde getirmektedir. Bu makale, lecanemab, aducanumab, edoksaban ve evolokumab gibi geriatrik hastalarda kronik hastalıkların tedavisinde kullanılan ve yakın zamanda onaylanan yeni ilaçları ele almaktadır.

Anahtar Kelimeler: Geriatri; adusanumab; edoksaban; evolokumab; lekanemab

The number of individuals aged 65 and older is expected to reach over 70 million by 2030 and 80 million by 2050 worldwide. Additionally, the population of individuals aged 85 and older will triple by 2050, which requires advancing the treatment modalities. Balancing care for the aging population entails the delivery of tailored, cost-effective treatments. However, this goal intersects with the demand for advanced therapies that extend life, limit diseases, and enhance the quality of life. This creates a challenge in managing high-cost treatments for prevalent chronic conditions in older adults, raising concerns about affordability and value. This underscores the evolving healthcare landscape's complexity, where innovative solutions and accessible care intersect, necessitating careful consideration of cost, benefit, and sustainability in ensuring equitable access for an aging population. Yet, treatment of chronic diseases in elder population involves challenges of the requirement of innovative treatments that prolong life, alleviate diseases, improve cognitive and functional decline, and enhance symptom management.[1]

Geriatric patients are prone to various chronic diseases and health conditions. These conditions can significantly impact their overall health and quality of life. Some of the common diseases in geriatric patients include hypertension, diabetes, osteoarthritis, asthma, visual problems, coronary artery disease, cerebrovascular events and cognitive diseases.[2,3] These chronic illnesses are common in the expanded elderly population which

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requires long-term treatment options with enhanced pharmacological effectiveness.[2] This review article focuses on recently approved novel pharmacological medications by The U.S. Food and Drug Administration (FDA) (Table 1) for the treatment of common geriatric diseases; lecanemab and aducanumab for Alzheimer's disease (AD), edoxaban for coagulations disorders, and evolocumab for hyperlipidemia.

LECANEMAB

Mechanism of action: Lecanemab (Leqembi, BAN2401) is a monoclonal antibody that targets amyloid beta (Aβ) species in the treatment of early AD.[4] Lecanemab reduces amyloid plaques in the brain and slow down clinical decline in patients with early AD.[4] The drug has been developed by fusing single-chain fragment variables to the N-terminal ends of the mAb158 antibody, resulting in improved binding strength to soluble aggregates of Aβ.[5] The binding properties of lecanemab to different forms of Aβ have tenfold stronger binding to Aβ protofibrils compared to fibrils. This unique binding profile of the drug might also be related to its clinical results including its efficacy and side effects.[6]

Indications: FDA has recently approved lecanemab for the treatment of adult patients with AD. This drug is the first amyloid beta-directed antibody to be converted from an accelerated approval to a traditional approval for the treatment of AD. Lecanemab is administered intravenously and the dosing regimen for AD is 10 mg/kg (actual body weight) once every 2 weeks.[7]

Clinical pharmacology: Lecanemab has been shown to reduce the rate of cognitive decline with a 27 % reduction in patients with AD.[8] In a phase 2 proof-of-concept study, lecanemab demonstrated robust brain fibrillar amyloid reduction and significantly slowing clinical decline in patients with early AD. The study also found that rapid and pronounced amyloid reduction correlated with clinical benefit and potential disease-modifying effects. In a phase 2 study, significant plaque reduction was observed with lecanemab, and the highest dose showed clinical benefit. Lecanemab has also been associated with the lowest rates of vasogenic edema among anti-amyloid antibodies.[4] Cerebrospinal fluid (CSF) biomarker analyses showed that lecanemab increased amyloid-related imaging abnormalities with edema (ARIA-E) and decreased p-tau compared to placebo. Amyloid-related imaging abnormalities-edema (ARIA-E) consistent with vasogenic edema and/or sulcal effusions or amyloid-related imaging abnormalities-hemosiderin deposition (ARIA-H) characterized by superficial siderosis and microhemorrhages (Ref) have been reported with lecanemab therapy. Patients may develop ARIA-H with concomitant ARIA-E. Most cases who developed ARIA-E during clinical trials were mild to moderate in severity; recurrent episodes have also been described. The incidence of ARIA-E was found to be well-tolerated in patients receiving lecanemab.[9,10] Advers effects such as headache, hypersensitivity reactions, atrial fibrillation and diarrhea might also developed in lecanemab-treated patients.[11]

ADUCANUMAB

Mechanism of action: Aducanumab is a human-derived monoclonal antibody that developed for the treatment of AD which selectivity binds aggregated forms of Aβ including

TABLE 1: Novel treatment options approved by FDA for chronic conditions.

Drug Name	Indication	FDA Approval Date	References
Rimegepant	Acute Treatment of Migraine	Approved in 2020	(32)
Lemborexant	Insomnia	Approved in 2020	(33)
Bempedoic acid	Hypercholesterolemia	Approved in 2020	(34)
Ozanimod	Relapsing Forms of Multiple Sclerosis (RMS)	Approved in 2020	(35)
Relugolix	Prostate Cancer	Approved in 2020	(36)
Inclisiran	Hypercholesterolemia	Approved in 2021	(37)
Vericiguat	Heart Failure	Approved in 2021	(38)
Voclosporin	Lupus Nephritis	Approved in 2021	(39)
Teplizumab	Disease-Modifying Therapy in Type 1 Diabetes.	Approved in 2022	(40)
Sparsentan	Focal Segmental Glomerulosclerosis (FSGS) And Iga Nephropathy	Approved in 2023	(41)
Sotagliflozin	Prevention Of Cardiovascular Death and Hospitalization for Heart Failure	Approved in 2023	(42)

soluble Aβ oligomers and insoluble amyloid plaques.[12] In addition to binding to Aβ aggregates, aducanumab's mechanism of action involves promoting Aβ clearance from the brain.[13] Clinical trials have demonstrated the efficacy of aducanumab in reducing the brain Aβ plaques and slowing clinical decline in patients with AD.[14]

Indications: FDA approved aducanumab for the treatment of AD in patients with mild cognitive impairment or mild dementia stage of disease, with the presence of amyloid beta pathology. Aducanumab is administered intravenously, and it is recommended to increase the dose every 4 weeks to titrate the highest dose of 10 mg/kg to maximize its efficacy over a 6-month period. Intravenous infusions are recommended to be administered at least 21 days apart.[15]

Clinical pharmacology: Clinical trials of aducanumab included patients with early AD who had confirmed brain amyloid using amyloid positron tomography. It is recommended to restrict the use of aducanumab to this population, as efficacy and safety have been studied in this specific group.[16,17]

Apart from the confirmed presence of amyloid beta pathology; patients with cognitive decline attributed to non-AD pathologies, such as Lewy body disease and vascular dementia, should not be offered aducanumab. Additionally, aducanumab is considered contraindicated in patients with a high risk of hemorrhagic side effects and unstable psychiatric conditions. Headache, falls, diarrhea, and confusion were also developed more commonly in aducanumab-treated patients compared to placebo controls.[18]

EDOXABAN

Mechanism of action: Edoxaban, along with other non-vitamin K antagonist oral anticoagulants (NOAC) like rivaroxaban and apixaban, selectively and reversibly inhibits free factor Xa and prothrombinase activity.[19] Which is responsible for the generation of thrombin. Edoxaban does not interfere with thrombin activity unlike thrombin inhibitors such as dabigatran which effectively reduces the risk of thromboembolic events.[20,21]

Indications: FDA approved edoxaban in 2015 for the treatment of venous thromboembolism (VTE; deep vein thrombosis and pulmonary embolism) and to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation following the initial anticoagulant therapy. Oral dosage of edoxaban is 60 mg once daily in patients over 65 years of age for the treatment of venous thromboembolism, post-percutaneous coronary intervention with stent placement and nonvalvular atrial fibrillation (AF) and to prevent stroke and systemic embolism. The dose can be reduced to 30 mg once daily for patients over 80 years of age who encompass some conditions and under high risk of using oral anticoagulants including low body weight, severe kidney impairment, history of bleeding, concomitant use of a nonsteroidal anti-inflammatory or antiplatelet drug.[22]

Clinical pharmacology: In terms of clinical effectiveness and safety rates of thromboembolism were approximately 2% for the 30 mg and 1.6% for the 60 mg edoxaban dose. The rates of bleeding were similar for both doses in patients with AF.[23] Comparison of efficacy and safety of edoxaban with warfarin and danaparoid sodium for the treatment of portal vein thrombosis (PVT) in patients with liver cirrhosis revealed that edoxaban was effective in preventing thrombus formation and had predictable pharmacokinetics in comparison with warfarin and danaparoid sodium.[24]

In a study investigated the drug-drug interactions of edoxaban, coadministration of edoxaban with P-glycoprotein (P-gp) inhibitors, such as quinidine, verapamil, and dronedarone was found to increase edoxaban effects. These findings suggest that coadministration of edoxaban with these P-gp inhibitors may increase the risk of bleeding.[20] In terms of drug interactions, one study evaluated the interactions between edoxaban and ketoconazole, erythromycin, and cyclosporine. The study found that co-administration of these drugs mildly increased the concentration of edoxaban, which did not result in clinically significant adverse events.[20,21]

EVOLOCUMAB

Mechanism of action: Monoclonal antibody evolocumab targets proprotein convertase subtilisin-kexin type 9 (PCSK9) to reduce low-density lipoprotein (LDL) levels and related cardiovascular events. After binding to PCSK9 evolocumab prevents PCSK9 from binding to the low-density lipoprotein receptor (LDLR). This inhibitory action leads to an increase in the number of LDLRs in hepatocytes, resulting in increased LDL clearance from the bloodstream.[25] By reducing the levels of LDL cholesterol (LDL-C), evolocumab has been shown to lower the risk of major adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death.[26]

The mechanism of action of evolocumab is distinct from that of statins, which are hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors. Evolocumab acts extracellularly by blocking the interac-

tion between PCSK9 and LDLR, while statins primarily inhibit cholesterol synthesis within cells. This difference in mechanism of action may account for the divergent effects of evolocumab and statins on postprandial triglyceride-rich lipoprotein (TRL) metabolism.[27]

Indications: Evolocumab was approved by the FDA in 2015 and it is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular diseases, for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia; HeFH) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) and homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL.[28]

Evolocumab can be administered 140 mg every 2 weeks or 420 mg once monthly via subcutaneous route for patients with primary hyperlipidemia, HeFM, and prevention of cardiovascular events in patients with established cardiovascular disease. For patients with HoFM drug can be administered 420 mg once monthly subcutaneously.[29]

Clinical pharmacology: A clinical study revealed that evolocumab significantly diminished the concentration of LDL particles (LDL-P) compared with placebo, along with the concentrations of medium very low-density lipoprotein particles (VLDL-P), small VLDL, and intermediate-density lipoprotein particles in patients with hyperlipidemia. The study also reported significant changes in the size of LDL, HDL, and VLDL particles with evolocumab treatment, suggesting the effectiveness of lowering atherogenic lipoprotein particles, including low-density and remnant lipoproteins.[30] Evolocumab was not associated with glycemia, beta cell function, or symptoms of new-onset diabetes, including changes in fasting plasma glucose, glycated hemoglobin, or weight compared with placebo and statin therapy, which has been associated with a modest increase in the risk of new-onset diabetes.[31]

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