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New Drug Update

Vamorolone: revolutionizing Duchenne muscular dystrophy treatment

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a severe inherited neuromuscular disorder characterized by a dystrophin gene mutation, leading to progressive muscle weakness and structural degradation. Current management strategies focus on multidisciplinary approaches to mitigate symptoms and enhance quality of life. Conventional glucocorticoids present challenges due to their complex nature and severe side effects. Vamorolone, a first-in-class dissociative steroidal drug recently Food and Drug Administration (FDA) - approved, distinguishes itself through enduring anti-inflammatory effects with reduced safety concerns. Pharmacologically, Vamorolone's mechanism of action, differentiating it from traditional corticosteroids, involves selective glucocorticoid receptor (GR) modulation and mineralocorticoid receptor (MR) antagonism, offering improved safety and tolerability. Notably, its unique Δ9,11 modification prevents adverse receptor interactions, demonstrating superior safety in inhibiting inflammation across various cell types. This article explores Vamorolone's pharmacokinetics, drug interactions, and adverse effects, underscoring its well-tolerated profile with reversible hypothalamic-pituitary-adrenal axis suppression as a notable concern. Comparative studies against prednisone reveal Vamorolone's efficacy in improving muscle strength with minimal side effects, validated through the pivotal Phase IIb VISION-DMD study. Ultimately, Vamorolone has attained a breakthrough status in DMD treatment. Its endorsement by the FDA underscores Vamorolone as a transformative linchpin, heralding a new era in revolutionizing DMD care.

Keywords: Duchenne muscular dystrophy, Corticosteroids, Glucocorticoids, Vamorolone

INTRODUCTION

Duchenne muscular dystrophy (DMD) is one of the most severe forms of inherited muscular dystrophies.[1] It represents the prevalent hereditary neuromuscular ailment distinguished by a mutation in the dystrophin gene, located on chromosome Xp21, which precipitates a gradual decline in muscle strength and structural integrity , leading to difficulties with movement and, eventually, to the need for assisted ventilation and premature death (usually occurs before 20 years).[1,2] It is inherited as an X-linked recessive trait (the estimated incidence is 1 in 3600 male live-born infants, females are carriers).[3] Mutations result in diminished production of the dystrophin protein (a protein that protects muscle fibers from breaking down when exposed to enzymes), ultimately resulting in erosion of the myofiber membrane integrity through recurrent cycles of necrosis and regeneration. Subsequently, fibrous connective tissue and adipose deposits progressively supplant muscle tissue, thereby giving rise to observable clinical manifestations. It is noteworthy that dystrophin is expressed not only in striated and cardiac muscle but also in the brain and the retina. Consequently, manifestations of DMD encompass cardiomyopathy, respiratory insufficiency (attributable to muscle weakness), and orthopedic complications, while certain cases may also present with central nervous system (CNS) manifestations of the ailment.[3]

While there is no known cure for DMD, current multidisciplinary approaches aim to manage the disease and its myriad of symptoms by decelerating symptom

progression to improve quality of life. The primary interventions include glucocorticoids, physical therapy, respiratory therapy, cardiac management, orthopedic interventions, and dietary considerations.[5] Glucocorticosteroids, frequently employed as anti-inflammatory agents, are the standard of care when there is motor decline. Their primary objective is to ameliorate impaired muscle function, avert deformities, and augment muscular strength.[2] However, the challenge with chronic glucocorticoid therapy lies in its multi-faceted nature, characterized by an elusive molecular mechanism and severe side effects that often impact patient compliance. These adverse effects encompass immunosuppression, growth inhibition, disturbances in glucose and fat metabolism, health issues, delayed puberty, and behavioral changes.[2,6] Vamorolone (AGAMREE®), a first-in-class dissociative steroidal drug, recently approved by the FDA, designed for DMD management, presents enduring anti-inflammatory and immunosuppressive effects that improve muscle pathophysiology and confer protection against cardiac failure.[7] This novel drug showed evidence of efficacy and reduction of safety concerns typically seen with traditional glucocorticoids.

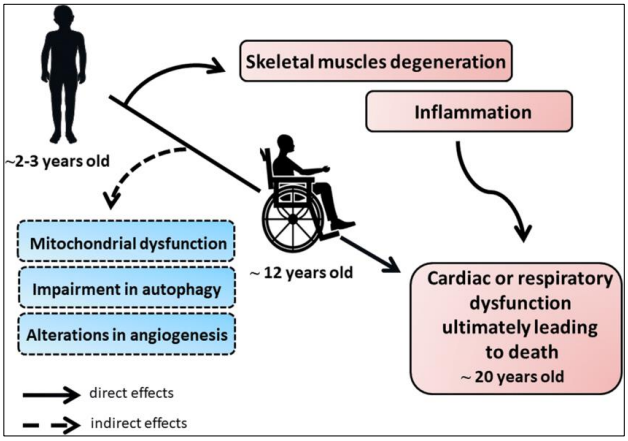

Figure 1: DMD progresses rapidly, starting in early childhood around ages 2–3, causing skeletal muscle degeneration due to dystrophin deficiency. This leads to muscle weakness and immune responses from cycles of muscle fiber degeneration and regeneration. By age 12, mobility is typically lost, and by age 20, cardiac or respiratory dysfunction leads to death. Research into potential pathways like m itochondrial dysfunction, impaired autophagy, and angiogenesis remains crucial due to the absence of a cure.[4]

PHARMACOLOGICAL CHARACTERISTICS

Mechanism of action

Vamorolone targets the same nuclear receptors as corticosteroids, known as the glucocorticoid receptor (GR), but it does not lead to glucocorticoid response element (GRE) transactivation, unlike traditional corticosteroids. GREs mediate the transcriptional pathways that lead to harsh side effects.[5] This distinctive dissociative characteristic of Vamorolone enables it to maintain efficacy without causing off-target effects, contributing to a significantly improved safety and tolerability profile over currently used steroids such as prednisone and deflazacort.[8,9] Additionally, Vamorolone serves as a mineralocorticoid receptor (MR) antagonist, reducing MR activity, which makes the drug beneficial in countering dystrophic cardiomyopathy and cardiovascular morbidity.[8]

How Vamorolone differs from other corticosteroids

MR and GR, while sharing common ligands, play distinct roles in dystrophic heart and skeletal muscle pathophysiology. Vamorolone differs from conventional glucocorticoids by lacking an 11β hydroxy-carbonyl group.[10] This unique Δ9,11 modification significantly prevents its interaction with a conserved receptor residue (N770/N564), averting the activation of transcription factor properties in both receptors.[9] Moreover, Vamorolone is not a substrate for 11β-hydroxysteroid dehydrogenase regulatory enzymes and acts as MR antagonists along with eplerenone, contrasting with prednisolone, an MR agonist.[10] Vamorolone, acting as a dissociative GR ligand, shows superior safety in inhibiting inflammation across macrophages, cardiomyocytes, and CRISPR knockout myoblasts compared to prednisone and GR-specific deflazacort.[9] Genetic dystrophin loss exacerbates MR-mediated cardiomyopathy in DMD model mice, with aldosterone worsening fibrosis, mass, and dysfunction. Vamorolone effectively prevents MR-activated phenotypes, whereas prednisolone activates negative MR and GR effects.[9] Therefore, Vamorolone maintains efficacy-associated subactivities (transrepression, physicochemical membrane effects, synchronization of tissue remodeling) while dissociating from those linked to adverse side effects.[10]

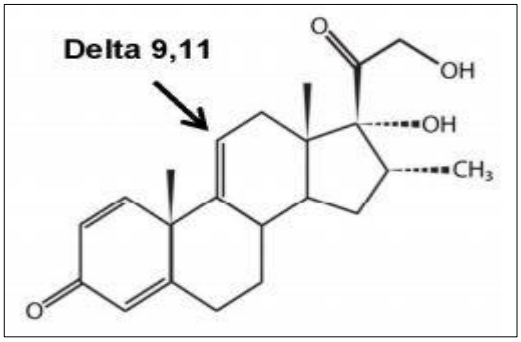

Figure 2: Structure of Vamorolone.

Adverse effects

Side effects associated with Vamorolone treatment greatly depend on its dosage. Most common include cushingoid features (7-29%), psychiatric disorders (7-21%), increased appetite (3-7%), vomiting (14-17%), increased weight (11%), vitamin D deficiency (7-11%), headache (7%), diarrhea (3-7%) and rhinitis (3-7%).[10] Vamorolone may

lead to reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, potentially resulting in secondary adrenal insufficiency after withdrawal. Hence, post-vamorolone withdrawal, monitoring for Cushing syndrome, hyperglycemia, and adrenal insufficiency is advised.[10]

Pharmacokinetics

The FDA has approved Santhera Pharmaceuticals' investigational agent Vamorolone (marketed as Agamree) oral suspension 40 mg/ml for the treatment of patients with DMD aged 2 years and older.[12] It exhibits maximum plasma concentration at approximately 2-4 hours (88.1% of which is protein bound) and a half-life of about 2 hours for all doses.[13] It is metabolized via multiple Phase I and Phase II metabolic pathways (glucuronidation, hydroxylation, and reduction) and majorly excreted in feces and urine with clearance averaging 1.7-2 L/h/kg.[13] Vamorolone demonstrates consistent linear Pharmacokinetics (PK) and absorption and disposition profiles that align closely with classical glucocorticoids.[13]

Drug interactions

Vamorolone when combined with other anti-inflammatory drugs (Aceclofenac, Acemetacin) can increase the risk of severe gastrointestinal (GI) irritation. It can also intensify anticoagulant activities of certain drugs like Acenocoumarol. Bioavailability and therapeutic effect of Vamorolone may decrease when combined with drugs like Aluminum hydroxide and vitamin D analogues.[14] However, overall, it is well tolerated in most individuals.

Vamorolone versus prednisone: optimizing muscle strength with minimal side effects

FDA's approval of vamorolone was based on data sourced from the pivotal Phase IIb VISION-DMD study (NCT03439670), further supplemented by safety information from three open-label studies, including extension studies.[15] The Phase IIb study is a randomized, double-blind, parallel group, placebo and active-controlled study to evaluate the efficacy, safety, pharmacodynamics (PD) and population PK of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg versus prednisone 0.75 mg/kg/day and placebo.[16] The study spans a 24-week treatment period, with an additional evaluation of the persistence of effect over 48 weeks in 121 ambulant boys aged 4 to <7 years with DMD. The study achieved its primary endpoint, demonstrating significant improvements in time to stand velocity (TTSTAND) from a supine position with 6 mg/kg/day of vamorolone compared to placebo ($p=0.002$).[6] Furthermore, secondary endpoints, including the 6-minute walk test and time to run/walk 10 m velocity, also favored vamorolone 6 mg/kg/day over placebo and efficacy was maintained in the 48-week extension phase.[7] The study assessed whether vamorolone improves muscle strength and function more effectively than placebo and with fewer side effects than prednisone. Vamorolone and placebo-treated patients demonstrated normal growth, contrasting with growth stunting observed in prednisone-treated children. Moreover, switching from standard corticosteroids to vamorolone preserved efficacy benefits while promoting growth and bone health recovery.[8]

In another nonrandomized controlled trial of 46 boys with DMD, higher dose vamorolone treatment for up to 30 months was associated with decreased adverse outcomes compared with traditional glucocorticoid therapy.[17] A Phase IIa open-label, multiple ascending dose study to assess the safety, tolerability, PK, PD, and exploratory efficacy of vamorolone in boys with DMD showed similar findings.[18]

CONCLUSION

DMD presents a complex challenge due to its progressive nature and profound impact on muscle function. While traditional glucocorticoid therapy has been the established standard, its associated side effects pose significant obstacles. Vamorolone has emerged as a notable breakthrough in DMD treatment, offering a promising alternative to conventional corticosteroids. Its unique dissociative properties promise enhanced efficacy while minimizing adverse effects. Evaluating the available evidence, Vamorolone exhibits comparable efficacy to other corticosteroids, yet with a more favorable side effect profile akin to glucocorticoids. In summary, Vamorolone holds great potential for transforming the treatment approach for individuals with DMD.

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