• Review Article •

Retardation of myopia by atropine regimes

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Received: 2023-11-20 Accepted: 2024-06-26

Abstract

● Myopia is a huge health problem due to its high frequency, vision losses and public health cost. According to the World Health Organization, at least 2.2 billion people have vision impairment. Although myopia can be controlled at its early and middle stages, unfortunately, no cure can be achieved so far. Among the methods to control myopia, atropine, a muscarinic receptor antagonist, is the oldest but still the most effective for retardation of myopia progression. Despite such a fact, standard protocols have not been established for clinicians to use atropine for treatment of myopia. In this article, a concise and up to date summary of myopia epidemiology and pathogenesis and summarized therapeutic effects and side effects, possible mechanisms and application methods of atropine were provided in hope for clinical doctors to effectively control this problematic disease. At present, the protocol is recommend: use higher dose (1%) of atropine intermittently to effectively slowdown myopia progression in schoolchildren for 2y, and to significantly reduce side effects of atropine by decrease of atropine frequency for 1y and inhibit myopic rebound by withdrawal of topical atropine gradually for 1y. Application of a lower dose (0.05%) atropine regime should also be considered due to its effectiveness and application at regular basis.

● **KEYWORDS:** myopia; myopia progression; atropine; schoolchildren

DOI:10.18240/ijo.2024.11.20

Citation: Zhu Q, Chen L, Liang JR, Hu M, Xue LP, Zhou GL, Zhou Y, Zhang JY, Fernandez-Hazoury D, Helman A, Zhu YT, Zhang XF. Retardation of myopia by atropine regimes. *Int J Ophthalmol* 2024;17(11):2129-2140

INTRODUCTION

Myopia is "nearsightedness" caused by a refractive error. That is, the eye does not refract light correctly. In myopia, the patients see the close objects clearly but distant objects blurrily. The common form of myopia is secondary to increase of the axial length (AL) in eyes, often termed axial myopia. Myopia usually becomes more severe in adolescent years and then stabilizes after the age of a young person reaches twenties. During this period, the risk of myopia damages is positively linked with AL growth. Thus, the effective method to decrease myopia damages is probably to retard myopia progression in early childhood[1-2].

Current evidence suggested that myopia progression largely depended on age, and that early onset means more progression because it continued for more years. The prevalence decreased with ages and increased with education level[3]. The factors critical to occurrence of myopia are too little time of outdoor activities[4], too much school work[5], too much near work[6], too many prenatal factors[7]. In addition, early onset of high myopia is closely linked to family inheritance[8]. Furthermore, the prevalence of myopia varies geographically (for factors associated with myopia[9]). For example, in Chinese children, the annual incidence of myopia in 7 to 12 old school children is about 8%–18%[4,10], compared to a much lower incidence of 2.2% in similar age school children in Australia[11].

The onset of myopia is low in rural areas, for example, in rural areas of Mongolia, where the incidence in 2006 was 6% in total of 1057 schoolchildren aged between 7 and 17y[12]. In Europe, education was significantly linked to myopia. For those who completed primary, secondary, and higher education, the prevalences were 25%, 29%, and 37%, respectively[13-14]. In USA, the incidence of myopia school children increased from 12.0% in 1971 to 31% in 2004[15]. In

addition, the environmental factors are also involved in school-age onset of myopia[8].

MYOPIA EPIDEMIOLOGY

Myopia is a huge problem for public health especially in Asia countries such as China[16]. Over past decades, the prevalence of myopia and high myopia is increasing significantly in children, for example, in East Asia[17-18]. From 1983 to 2000, the incidence of myopia in 7-year-old school children has increased significantly, from approximately 6% to around 21.0% in Taiwan, China[17]. In East Asia metropolitan areas, up to 90% of secondary school children have suffered from myopia, in which approximately 20% of those children have suffered high myopia[19]. Overall, the prevalence of myopia has elevated from 80% to 88%, including increase of moderate myopia from 39% to 46%, severe myopia from 8% to 17%, and terminal myopia from 0.1% to 0.9%[20]. In China, the overall myopia rate among children and adolescents in 2022 is 51.9% (36.7% in primary schools, 71.4% in middle schools, and 81.2% in high schools), which has dropped by 0.7 percent compared to 2021 (52.6%), by 1.7 percent compared to 2018 (53.6%), among whom mild, medial and high myopia account for 53.3%, 37.0%, and 9.7% respectively (https://www.ndcpa.gov.cn/jbkzzx/c100008/common/content/content_1764617954927783936.html). In addition, the prevalence percentage is 80% in the young people from areas such as Hong Kong, Singapore, and Taiwan[17,21]. Although in USA, the prevalence rate is from 20% to 50% in the young population greater than 12 years old[22], it is still a relatively large epidemic incidence[23]. Unfortunately, high myopia is a main cause of untreatable blindness in this world, usually because of irreversible damages to eyes, for example, choroidal neovascularization, macular degeneration, retinal detachment and break and as a results, glaucoma[24-27]. The risk of these damages is positively associated with the stages of myopia and the earlier the onset of myopia in childhood is, the worse the myopia is in an adult life[28-31]. According to the World Health Organization, at least 2.2 billion people have a vision impairment, causing significant social problems[32], high economic burden worldwide, and even complete blindness due to other ocular problems, including macular degeneration, glaucoma, Parkinson's disease and obstructive pulmonary diseases[33]. Several clinical methods have been applied to retard myopic progression[34-37] (also reviewed in Russo *et al*[38]). However, standard protocols have not been established for control of myopia[39] (for recent reviews of atropine on control and prevention of myopia[40-50]).

Although efforts have been made for establishment of an effective protocol for treatment of myopia worldwide by clinicians, many questions remain to be addressed, for example, what are significant gaps in knowledge and practice in controlling myopia by atropine and optical treatments[51]. Summary of current knowledge of etiology and possible control methods in myopia is also published recently[52-53].

PATHOLOGICAL CHANGES IN MYOPIA

The emmetropization is a process by which the refraction of the anterior ocular segment and AL of the eye tend to balance each other to produce emmetropia. Myopization is an abnormal increasing process of the emmetropization. The axial elongation is linked to thinning of the choroid, the sclera[54], the retina and decreased retinal pigment epithelium cells density in retro-equatorial area[55-57]. Eyes suffering from retinopathy of prematurity treated with anti-vascular endothelial growth factor (VEGF) drugs has been reported to relieve axial myopia[58]. Injection of apomorphine, a dopaminergic agonist, may cause significant inhibition of ocular growth in a lens-induced model of myopia[56,59]. An anticholinergic agent, pirenzepine, acting on muscarinic M1 receptor, may selectively retard axial elongation in guinea pigs and monkeys if injected intravitreally[60-62]. The prevention of abnormal scleral remodeling is an important goal of long-term therapy for amelioration of the severe vision loss linked to high myopia[59,63]. Up to now, atropine is still the effective medication to retard myopic pathological changes, and thus progression[34,64].

When myopia occurs in a child, the progression rate is approximately -1 D a year in East Asians and about -0.5 D a year in Caucasians[65-66]. After a few years, many children will progress to the level of high myopia. Therefore, it is very important for us to prevent myopia progression in myopic children as soon as possible. Certainly, control of myopia has the following advantages: to obtain better visual performance; to avoid serious eye damages, pathological changes and resultant surgeries, which do not necessarily correct deficit of eyes suffering myopia; to reduce visual[67].

ATROPINE CONTROL OF MYOPIA

Up to now, choices for the control of myopia include contact lenses[68], multifocal soft contact lenses[69], peripheral defocusing lenses[34], progressive executive bifocal spectacle lenses[70-72], overnight orthokeratology[73-75], orthokeratology lenses[76-78], outdoor exercises[79] and pharmacological drugs[80], and their combinations[81-82] (also reviewed in Zhu *et al*[83]). One recent report suggested that orthokeratology was better than 0.01% and 0.05% atropine for treatment of anisomyopia in children in a comparative two-year investigation[84]. However, it was controversial because another recent report indicated that multiple lenses, spectacles and contact lenses, better than single lenses, only provides small beneficial effect on control of myopia while atropine was effective in controlling children's myopia progression[85]. In fact, use of bifocals, contact lenses and progressive addition lenses are not that effective in myopia control[34] (not all agree, for example in Medina[86]). In contrast,

pharmacological treatment by atropine is popular because the results from atropine treatment of children's myopia is effective[87-92]. Indeed, atropine, an anticholinergic blocking agent, is most effective for retarding myopia, though the actual mechanism of its pharmacological action remains unclear even some possible biological pathways by atropine are proposed[93]. These investigative pharmacological studies have clearly demonstrated that topical atropine is effective in retarding low and moderate myopia and slowing AL elongation in Asian school children.

Although atropine is effective for control of myopia, it is still controversial what is the optimal dose, application methods, effectiveness and side effects for this medication to retard myopia without serious side effects[34,64,94-96]. Studies have shown that the side effects of atropine have a dose effect, and as the concentration of atropine decreases, the side effects are reduced[97-98]. At present, various concentrations of atropine such as 1%, 0.5%, 0.1%, 0.05%, 0.125%, and 0.01% are used for this kind of studies[99]. Among the doses, 0.05% atropine is relatively effective without significant rebound[99-101].

Chia *et al*[98] treated patients with myopia with 0.5%, 0.1%, and 0.01% atropine for 2y. The progression of myopia was inhibited by -0.30±0.60 D, -0.38±0.60 D, and -0.49±0.63 D respectively, showing that the effect of 0.01% concentration of atropine on myopia was not statistically different from that of 0.5% or 0.1% atropine. One year after discontinuation of each concentration of atropine, refractive retraction occurred in each group, especially in the higher concentration atropine group. Based on the results of the entire follow-up period, 0.01% atropine group showed better control effects with fewer side effects than 0.5% and 0.1% atropine groups[98]. That is, the lower the concentration of atropine, the better the control effect and the less adverse drug reactions. In fact, many studies have focused on 0.01% atropine for the control of myopia for a long time, even until recently[102-110]. In addition, after the withdrawal, the withdrawal symptoms are more serious in higher concentration of atropine[98]. Furthermore, concerns about the possible long-term side effects of 1% atropine eye drops have increased, including phototoxic effects on the retina and lens, near vision blurring, photophobia, allergic reactions, and myopia rebound after termination of the treatment[89]. That is why low concentrations (such as 0.01%) atropine have been widely used previously despite less effective results in the myopia control because adverse reactions and refraction are mild after withdrawal[102]. Nevertheless, researchers have gradually questioned the atropine efficacy of 0.01% or 0.02% atropine due to its low effectiveness[111-114].

The high concentrations of atropine, for example, 1% or 0.5%, are remarkably effective in slowing myopia progression. However, the high incidence of side-effect, for instance, photophobia, may occur, depending on clinicians' protocols[88,95,115-116]. In addition, there are concerns regarding potential long term systemic or ocular side effects. Furthermore, there are also concerns on the rebound effect after atropine discontinuation, especially in high concentration of atropine, for instance, 1% atropine[49,95].

Atropine has dose-dependent efficacy for controlling myopia, with effective incidence of 78% in 1% atropine group, 75% in 0.5% atropine group, 70% in 0.1% atropine group and 50% in 0.01% atropine group[89,98]. Most recently, we have shown that we can achieve high efficiency of 1% atropine in slowing progression of myopia, at the same time, reduction of side effects, for instance, photophobia and near vision blurring led by daily 1% atropine usage, and minimization of myopic rebound led by sudden termination of atropine, by use of 1% atropine once a month, once an eye alternatively in stage I of two years designated as the treatment period, once 2mo, once an eye alternatively in stage II of one year as the transition period, and withdrawal of atropine in stage III of one year in Chinese school children[95]. In our study, the frequency and method of use for 1% atropine was decreased from daily use in previous studies[95] in the first two stages, in which alternate eyes were treated monthly then bimonthly over three years, to minimize the side effects followed by withdrawal over one year, while maximizing efficacy at controlling myopia. Our results showed that after phase I, the mean progression of myopia was remarkably reduced in atropine group compared to that in control group [-0.45 D (-0.225 D/y) compared to -1.94 D (-0.97 D/y)]. Increase of AL in atropine group was also reduced compared to that in the control group [(0.25±0.31 mm) compared to (0.81±0.39 mm)][95]. Our results also demonstrated that increase of AL and myopia progression were reduced by 77% and 69% respectively when 1% atropine was used[95], resembling previous reports that daily 1% atropine reduced elongation of AL and progression of myopia by 70% and 78% in earlier reports[89-90,92,98,117]. Since 1% atropine was applied only to one eye at a time and alternatively, monocular near vision blur could be compensated by the other eye without atropine[95]. Therefore, we recommend this protocol to doctors for treatment of myopia in clinics worldwide. Our recommendations are: 1) identify risk factors and provide detailed advice to myopia patients; 2) treat high risk patients with atropine 1% and prescribe photo chromatic glasses to the patients; 3) follow up the patients with examinations for AL, visual acuity, cycloplegic refraction and reading acuity; 4) when spherical equivalent and AL are stable for one year, gradually withdraw 1% atropine as recommended[95]. Long term treatment of 1% atropine for control of myopia without significant complications is supported by a recent publication[118].

The strength for our 1% atropine regime includes high efficacy, low application frequency (easy to apply), mild side effects without a significant rebound on withdrawal of 1% atropine. The drawback is additional efforts needed, for example, prescription of lenses for prevention of reading problems, and more attention to patients needed right after application of 1% atropine. In addition, 77% to 93% injected atropine was excreted to urine in 24h[119]. Therefore, it is removed from the system rather quickly. We also do not know if atropine is sequestered in some way. Therefore, additional efforts are needed for explaining how the human bodies retain certain atropine in a long term, such as a month or two. Furthermore, whether regular-basis application of atropine is preferable than our long-term application remains debatable.

As we have indicated, targeting refraction change in myopia by atropine is effective to retard myopia progression[95]. Therefore, atropine is an example in clinical practice for controlling myopia[34]. Other reports support our point of views. For example, in a randomized clinical trial from Taiwan China, the authors demonstrated that 1% atropine is effective in retarding myopic progression when compared to placebo or 1% cyclopentolate in a one-year follow up observations[116]. The mean progression of myopia per year was -0.22±0.54 D in 1% atropine group, compared to -0.91±0.58 D in placebo group, and -0.58±0.49 D from 1% cyclopentolate group. In the other randomized trial, 0.5, 0.25, or 0.1% of atropine were tested for treatment of myopia in 6–13 years old children using tropicamide as controls in a 2-year follow-up study[65]. After 2y of follow-up, atropine groups were effective with cessation percentage of 61%, 49%, 42%, and 8% in 0.5%, 0.25%, and 0.1% atropine and the control groups. In addition, a lower percentage of rapid progression in children was observed in atropine treated than the control groups, that is, 4%, 17%, 33%, and 44% respectively, suggesting higher dose of atropine is more effective for retardation of myopia.

For example, authors recommended higher dose such as 0.02% and 0.05% atropine for more effective retardation of myopia than 0.01% atropine respectively[76,120-123]. Importantly, in a randomized trial of 0.05%, 0.025%, and 0.01% atropine on control of myopia, the authors concluded that 0.05% atropine was the best for controlling spherical equivalent progression and AL elongation in a one year trial[121], which is supported by another similar trial, with age-related effect[124]. In a subsequent two-year phase 2 trial, the authors draw a conclusion that 0.05% atropine for controlling myopia is two times better than 0.01%[122]. In a recent low-concentration atropine for myopia progression (LAMP) trial, the authors indicated that atropine at low concentrations can result in choroidal thickening linked to reduced AL elongation as well as spherical equivalent progression[125]. These studies support our decision to use 0.05% atropine for our investigation because 0.05% atropine is the best among doses of 0.01%, 0.025%, and 0.05% atropine, supported by a phase II, III, and IV LAMP study[126-128]. Our recent published article also supported that 0.05% atropine was an effective dose for controlling myopia[129], similar to a recent publication[130]. Therefore, we believe this regime may be an effective alternative regime for controlling myopia (for benefits and drawback of low dose atropine to control myopia (reviewed in Jonas *et al*[131]).

A 3-year study of atropine on controlling myopia in Europeans has demonstrated that a concentration of atropine at higher than 0.5% may retard myopia progression, supporting the finding that an increased dose to 0.5% but not as high as 1% of atropine was an option for effective treatment of myopia[132]. For high myopia patients, orthokeratology was better to control AL elongation than 0.02% atropine in a 2-year trial[133]. Therefore, it is suggested that 0.5% to 1.0% concentrations of atropine may better control myopia if the side effects are mitigated by an appropriate clinical protocol[134]. Currently, approximately 30 registered clinical trials of atropine, in the concentrations between 0.005% and 0.05%, are in their processes, which should be informative for better myopia control without rebounding after discontinuation of atropine[135]. Clearly, it is evident that from clinical practice, clinicians are preferring to use 0.05% atropine rather than 0.01% atropine in order to enhance the effectiveness of atropine for retarding myopia without significant rebounding after termination of atropine[135].

Significant elongation in the globe contributes a great deal to the degenerative myopia[136]. In a previous study, 188 school children were treated with or without 0.5% atropine in addition to multi-focal spectacles[137]. After followed up for 18mo, AL increase in the atropine group was remarkably inhibited than that in the group without atropine[137]. In fact, atropine, especially when used in high concentrations, for example, in 0.5% and 1% concentrations, is effective in retarding AL elongation in myopic eyes. For instance, AL increase in the atropine for the treatment of childhood myopia (ATOM 1) trial was 0.02±0.35 mm in the 1% atropine group after 24mo of study[89]. In contrast, AL increase was 0.38±0.38 mm in the control[137]. Interestingly, after 3y of study, AL increase was 0.29±0.37 mm in the 1% atropine group, in contrast to the control with an increase of 0.52±0.45 mm[91]. In ATOM 2 trial, AL increase after 2y of the study was 0.27±0.25 mm in 0.5% atropine group, 0.28±0.28 mm in 0.1% atropine group, and 0.41±0.32 mm in 0.01% atropine group, suggesting that higher dose of atropine is more effective[138-139]. In fact, high concentration atropine (1%) was more effective than low concentration atropine (0.01%) in retarding AL increase with effective percentage between 70% and 94% in a few clinical

trials[89,95,98,116,137,140-141]. Despite reports suggesting that side effects, including problems with near work and photophobia, no serious side effects were recorded even in long trials for more than 10y[142-144]. In addition, the results from electroretinograms of eyes treated with atropine suggested minimal damage to the retina in patients with daily usage of atropine[138-139] and no measurable difference in intraocular pressure between eyes using atropine or placebo[145]. Despite these facts, difficult near work and photophobia is still main concerns in patients with higher doses of atropine[116-117]. The other concern for atropine is rebound of myopia after cessation of atropine in high doses[87,91]. Therefore, because low dose (0.01%) atropine may decrease certain side effects and retard rebound of myopia[102], 0.01% atropine was recommended for treatment of myopia and prevention of pre-myopia to myopia[102,146-148]. Probably due to low effectiveness in the nature of pure 0.01% atropine therapy for myopia, a combined therapy of 0.01% atropine with orthokeratology in a two-year trial was reported, *via* retarding axial elongation for controlling myopia[149]. The results are supported by recent reports, which suggested 0.01% atropine, combined with orthokeratology, can improve myopia control by improved optical effect, probably due to a bigger photopic pupil size and enhance efficacy[150-157], and by a Meta-analysis, which indicated that combinations of orthokeratology with 0.01% atropine was more effective than orthokeratology alone for treatment of myopia by retarding axial elongation in a short duration of treatment, and the combination treatment does not have significant side effects on intraocular pressure, corneal endothelial density and distant visual acuity[158]. Meta-analyses also demonstrated that combinations of atropine with orthokeratology or the defocus incorporated multiple segments (DIMS) lens was effective for delaying axial elongation in children with myopia, better than orthokeratology alone[159-161] (for review of combinations of atropine and orthokeratology to control myopia control[99,162]). However, recent reports showed that 0.01% atropine alone was effective in controlling AL elongation[163] and myopia progression with or without spectacles or orthokeratology lenses[164]. In contrast, a report suggested that spectacle lenses and orthokeratology were better than 0.02% atropine for control of AL elongation[165], and combination of contact lenses and 0.05% atropine can better control myopia[166]. Although combination of orthokeratology with low-dose atropine is effective and synergistic, such complications may also have synergistic side effects[167]. Therefore, more investigations are required for whether such combinations are really good for retarding myopia with minimal side effects.

POSSIBLE MECHANISMS

Atropine sulfate, as eye drops, is an antimuscarinic receptor drug, acting on all muscarinic acetylcholine M1-M5 receptors. The ester structure is responsible for its activity[168]. In clinical applications to eyes, atropine is usually used topically from 0.01% to 4% concentration, in which the most commonly used dose is 1%[168]. The purposes of topical usage of 1% atropine are usually to dilate pupil (mydriasis) and to paralyze ciliary muscle (cycloplegia) for loss of accommodations. In addition, atropine eye drops are used for treatment of myopia[95], amblyopia[169], near-reflex spasm[170-171]. However, the accurate mechanism remains unclear[38,53,172-173].

Although its mechanism of actions is still unclear, a few possible speculations have been raised in previous decades[53]. Earlier investigations have suggested that atropine acted through cycloplegic action at smooth ciliary muscles to diminish accommodative eye reactions[174]. Nevertheless, animal studies did not support those hypotheses because damaging optic nerve[175] and Edinger-Westphal nucleus[176] did not affect development and recovery in experimental myopia models, which suggested that atropine should exert its actions *via* signaling transductions rather than accommodations. Because muscarinic antagonists, for example, atropine may induce transient choroidal thickening[125], it was believed that thickening of the choroid was associated with ocular growth mechanistically[177]. Interestingly, muscarinic receptors are present in retinal pigment epithelium, which might act as signaling cascades to affect the target tissue, for instance, choroid and sclera[178-179].

Atropine can stimulate dopamine release[180-181]. Dopamine is a neurotransmitter, which may be produced by retinal dopaminergic amacrine and interplexiform cells[182-183]. Dopamine level may stimulate fluctuations of postnatal ocular growth, such as anterior chamber depth, AL, choroid thickness as well as vitreous chamber depth[184-185]. In addition, retinal dopamine release can be stimulated by experimental induction of myopia in chicks, guinea pigs and tree shrews[186-188]. Such dopamine may be metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC)[189], and reduction of retinal dopamine levels may be due to reduced dopamine production[190]. Some investigations have shown that nonselective dopamine receptor agonists, for example, apomorphine, or dopamine itself and its precursor may decrease form-deprivation myopia (FDM) and lens-induced myopia[56]. These findings suggested that dopamine regulated protective effects from bright light in myopia pathogenesis. Dopamine receptors were found in retinal cells[191]. D1 receptors may promote cyclic adenosine monophosphate (cAMP) production through activation of adenylyl cyclase, while D2 receptors may inhibit cAMP production[192]. In addition, use of dopamine agonists may protect normal vision against FDM by activation of D2 receptors, while use of D2 antagonists may attenuate the protective effect[193]. Interestingly, D2 receptors may inhibit

dopamine agonists in FDM as well as lens-induced myopia, better than D1 receptors[177]. Although effectiveness of atropine to slow myopia is in black and white, it is still unclear what signal cascades triggered by atropine are to retard myopia.

Recently, a review summarized how myopia can be controlled by drug atropine, orthokeratology, near addition spectacle lenses, and soft multifocal lenses and dual-focus contact lenses and how their plausible mechanisms have recently been believed, including the factors influencing the growth of AL, the occurrence of refractive error, and the methods of myopia interventions[194]. In addition, although optical interventions can reduce progression for myopia, however, investigations are needed in mega studies with long-term duration, along with their studies of mechanisms[134]. It is plausible that use of combinations of optical and atropine may enhance efficacy of myopia control[195-196].

PROPSPECTIVE FOR USE OF ATROPINE IN CONTROL OF MYOPIA

Up to date, atropine as an anticholinergic blocking agent, is an effective agent for control of myopia worldwide. Although the mechanism of its action is still unclear, atropine appears act at its receptors to achieve significant medical benefit for control of myopia progression. Currently, there is an urgent need to reveal the exact mechanism of action in order to develop a drug with significantly improved efficacy and minimized adverse effects. In addition, there is also a need to identify new drugs to treat myopia, especially those resisting to atropine treatment.

CONCLUSION

In summary, this article provides a concise summary of atropine myopia epidemiology and pathogenesis, therapeutic effects and side effects, possible mechanisms. We recommend our 1% atropine regime and its application to control myopia. Other atropine regimes, particular 0.05% atropine regime, may also be considered for control of myopia.

ACKNOWLEDGEMENTS

Foundation: Supported by the Basic Research Fund for Science and Technology Department of Yunnan Province and Kunming Medical University (No.202401AY070001-289).

Conflicts of Interest: Zhu Q, None; **Chen L,** None; **Liang JR,** None; **Hu M,** None; **Xue LP,** None; **Zhou GL,** None; **Zhou Y,** None; **Zhang JY,** None; **Fernandez-Hazoury D,** None; **Helman A,** None; **Zhu YT,** None; **Zhang XF,** None.

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