State-of-the-Art Clinical Results of Growth Hormone Secretagogues, SARM and Antagonists

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Abstract

Introduction: The term growth hormone secretagogues (GHS) encompasses compounds that were developed to increase growth release of growth hormone (GH). GHSs include growth hormone receptor secretagogue agonists (GHS-R), whose natural ligand is ghrelin, and growth hormone releasing hormone (GHRH) agonists, to which GHRH binds as a native ligand. In the context of selective androgen receptor modulators (SARM), the presence of a Toll-IL-1 receptor domain (TIR) predicts a role for SARMs in innate immunity. SARMs are an emerging class of therapies aimed at cachexia, sarcopenia and hypogonadism or treatment of stress urinary incontinence, osteoporosis, breast cancer and Duchenne muscular dystrophy. **Objective:** To present the state-of-the-art scientific evidence in humans on the use of growth hormone secretagogues, SARM and antagonists. **Methods:** Experimental and clinical studies were included (case reports, retrospective, prospective, randomized studies and systematic review) with qualitative and/or quantitative analysis. For further specifications, the description "Clinical Trail" for refinement was added during the research, following the rules of the systematic review-PRISMA. Of 384 articles, a total of 80 articles were evaluated in full and 58 were included and discussed in this study. **Results and conclusion:** Several clinical trials have been conducted and completed to assess the safety and efficacy of GHS for the diagnosis and / or treatment of GH deficiency. Over the past two decades, scientists' efforts have focused on the discovery and biological characterization of new tissue-specific SARM to promote the beneficial effects of androgens with greatly reduced undesirable side effects. In this regard, numerous studies with SARM of different structures have been reported. Despite evidenced clinical and preclinical studies, no SARM has yet received full clinical approval.

Keywords: Growth hormone secretagogues. Peptides. SARM. Antagonists. Clinical Studies.

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INTRODUCTION

The term growth hormone secretagogues (GHS) encompasses compounds that were developed to increase the growth release of growth hormone (GH). GHSs include growth hormone receptor secretagogue agonists (GHS-R), whose natural ligand is ghrelin, and growth hormone-releasing hormone (GHRH) agonists, to

which GHRH binds as a native ligand [1]. Several GHS was developed to treat or diagnose GH deficiency, namely, growth retardation, gastrointestinal dysfunction, and changes in body composition, in parallel to extensive research to identify GHRH, GHS-R, and ghrelin [1].

Ghrelin is a polypeptide containing 28 amino acids that are mainly synthesized in the stomach. Its activity stimulates GH secretion and appetite, resulting in net body weight gain [1]. From a historical angle, growth hormone-releasing peptides (GHRPs) were found before the discovery of ghrelin and the ghrelin receptor. Subsequently, GHSs, that is, ghrelin peptide mimetics, were developed. It was only later that the GHS type 1 receptor (GHS-R1a) was discovered. Finally, ghrelin was successfully isolated as a natural GHS-R1a ligand from stomach substrates in 1999. This context triggered the development of ghrelin receptor agonists, GHRPs, and GHSs; some of which have reached tests in clinical trials [2-5].

A wide range of ghrelin receptor agonist indications has been evaluated including growth retardation, gastrointestinal dysfunction, and altered body composition; some of which have received approval from the Food and Drug Administration (FDA) [6-9]. The present study focused on the history of research and the pharmacology of ghrelin receptor agonists [10-13]. Publicly released clinical trials on GHSs will be discussed in this regard [14-18].

Also, in the context of selective androgen receptor modulators (SARM), the presence of a Toll-IL-1 receptor domain (TIR) predicts a role for SARMs in innate immunity, but SARM is very different from other TIR proteins mammalian cytosolic MyD88, Mal, TRIF and TRAM, as it is not necessary to signal downstream of Toll-Like (TLR) receptors [45]. Mammalian SARM was first described in 2006 as an inhibitor of TLR signaling. Another important role for SARM is in mediating cell death [45].

Also, a recent advance reveals that SARM is enzymes that degrade NAD + and this activity is necessary for SARM to perform axonal destruction of neurons [45]. Since SARM is the only protein in the TIR domain that exhibits this activity, this suggests that at some point in the early evolution the functions of the other TIR proteins diverged [45].

In this context, SARMs are an emerging class of therapies aimed at cachexia, sarcopenia, and hypogonadism or treatment of stress urinary incontinence, osteoporosis, breast cancer, and Duchenne muscular dystrophy [46]. Since their initial scientific reports in 1998 [46], SARMs with a variety of chemical supports and pharmacological profiles have been discovered to facilitate the selective activation of androgen receptor (RA) tissues. RA is a member of the steroid receptor family of ligand-activated transcription factors, which are crucial to the organogenesis, physiology, and pathology of many tissues and are activated by comprehensive ligands such as natural hormones, peptides, synthetic molecules or hormones from growth [46].

The ability of SARMs to promote muscle and bone growth and strength, inhibit the growth of breast cancer and shrink the prostate in animals and humans is a problem based on many parameters, such as differences in the conformation of RA, expression of the enzyme metabolizer of RA and steroids between tissue recruitment, co-activator, and co-repressor [47,48].

The present work aimed to present the State-of-the-Art of scientific evidence in humans on the use of growth hormone secretagogues, SARM, and antagonists.

METHODS

Experimental and clinical studies were included (case reports, retrospective, prospective, randomized studies, and systematic review) with qualitative and/or quantitative analysis. Initially, keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and then verified and validated by the MeSH system (Medical Subject Headings, the US National Library of Medicine) to achieve a consistent search.

MeSH Terms

The main descriptors (MeSH Terms) used were "Growth hormone secretagogues, Peptides, SARM, Antagonists and Human Studies". For further specifications, the description "Clinical Trail" for refinement was

added during the research, following the rules of the systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-https: //www.prisma-statement.org/).

The bibliographic search was carried out through online databases: PUBMED, OVID, COCHRANE LIBRARY, SCOPUS, PERIODICOS.COM AND GOOGLE SCHOLAR. The deadline and related research were set, covering all available literature on virtual libraries.

Series of Articles and Eligibility

384 articles were found involving studies in vitro, in animals, and humans. Initially, the existing title was excluded and duplicated according to the interest of only evaluating studies in human beings. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 80 articles were evaluated in full and 58 were included and discussed in this study.

Flow chart

GROWTH HORMONE SECRETAGOGUE

Results of major clinical studies and current status

The results of the main clinical trials and the current status of each GHS are summarized (**Table 1**). Several clinical trials have been conducted and completed to assess the safety and efficacy of GHS for the diagnosis and/or treatment of GH deficiency. The following are the main secretagogues found in clinical studies.

Sermorelin

Sermorelin was initially developed as a diagnostic tool for GH deficiency [23]. Sermorelin increased GH release rapidly and specifically in healthy children, but not in those with GH deficiency, compared to existing provocative tests, resulting in approval for this indication by the FDA in 1990 [24]. Subsequently, the 6-month treatment with sermorelin showed a significant increase in GH release and growth speed in children with GH deficiency [25,26], and preliminary data suggested the efficacy of treatment with sermorelin for 36 months [24]. Based on these findings, sermorelin was approved by the FDA for the treatment of idiopathic GH deficiency in children with failed growth in 1997.

Sermorelin has also been tested in other clinical indications, namely, loss of muscle mass in the elderly with GH insufficiency, lipodystrophy in HIV-infected patients, and impaired cognition in the elderly [27]. The results looked promising, but the development has not yet been completed. It was reported. Also, sermorelin was discontinued by EMD Serono in 2008, due to problems with the supply of the active ingredient.

Examorelin

Examorelin has reached Phase II clinical trials for the treatment of GH deficiency and congestive heart failure, but the results have not been released. Finally, Mediolanum Farmaceutici halted the production of the examorelin for strategic reasons in 2005 [13].

Tabimorelin

Tabimorelin did not show beneficial effects on GH release in adult patients with GHD in a Phase II study [17]. Also, tabimorelin has been reported to inhibit CYP3A4, which can lead to unexpected side effects [18]. To overcome this disadvantage, Novo Nordisk has developed some compounds derived from tabimorelin, such as NNC-26-1167, although they have not yet been evaluated in clinical trials.

Pralmorelin

Plasma GH levels after a single administration of pralmorelin were greater than 15 μg / L in healthy subjects, while less than 15 μg/L in patients with severe GHD 20, which led to the approval of pralmorelin for the diagnosis of GHD in Japan 2004 [28]. Also, pralmorelin has been shown to stimulate growth speed after 8 months of intermittent therapy in children with GHD with intact hypothalamic-pituitary (H-P) axes [28]. Although pralmorelin has reached Phase II clinical trials for the treatment of short statues, development

has been halted. This was probably because pralmorelin did not increase plasma GH levels sufficiently in patients with GHD.

Macimorelin

A Phase III clinical trial showed that oral macimorelin was effective for the diagnosis of adult GHD with 82% sensitivity and 92% sensitivity at an ideal cutoff point of 2.7 GH / mL, comparable to the GHRH and arginine test [29]. Another phase Clinical trial III was completed in 2016, to compare its effectiveness with the insulin tolerance test (ClinicalTrial.gov Identi fi c: NCT02558829), and AEterna Zentaris announced the search for the approval of macimorelin for this indication by the FDA and by the European Medicines Agency in March 2017. A Phase II clinical study for the treatment of cancer cachexia is also underway (ClinicalTrial.gov Identi fi rer: NCT01614990).

Gastrointestinal indication: Ipamorelin, Ulimorelin, relamorelin and TZP-102

Ipamorelin

Ipamorelin was introduced in Phase II clinical trials for the treatment of intestinal pseudo-obstruction (POI), sponsored by Helsinn Therapeutics. However, in patients undergoing intestinal resection, ipamorelin does not shorten the time for the first meal intake compared to placebo [30]. The Phase II clinical trial below showed no significant difference in measurable colonic functions between ipamorelin and placebo [31]. Due to these disappointing results, its development was halted.

Ulimorelin

Based on the favorable effects of ulimorelin on gastrointestinal function in animal experiments and small clinical studies, ulimorelin has progressed to randomized clinical trials for the treatment of diabetic gastroparesis or POI. In patients with diabetic gastroparesis, ulimorelin improved gastrointestinal symptoms, such as vomiting and loss of appetite, while there were no significant differences in improving gastrointestinal function between patients with IP who took ulimorelin and those who took placebo [32]. For this reason, efficacy and the risk of unexpected hypotension, its development for gastrointestinal indications has been discontinued [33].

Relamorelin

A Phase I clinical trial showed that relamorelin, compared with placebo, greatly accelerated gastric emptying in patients with diabetic gastroparesis. Subsequently, a Phase II clinical trial demonstrated that relamorelin significantly reduced the frequency of vomiting and improved gastric emptying in patients with diabetic gastroparesis [34]. These results allowed the FDA to grant a rapid appointment for relamorelin for the treatment of diabetic gastroparesis in 2016.

The safety and efficacy of relamorelin in chronic constipation were also assessed. In the Phase II clinical trial, relamorelin significantly reduced symptoms of constipation and accelerated colonic transit in female patients with chronic constipation [35]. Also, the same study showed that relamorelin rapidly increased colonic contractions without any change in irregular fundus contractions. These promising effects of relamorelin in gastrointestinal disorders may lead to a wide range of clinical applications soon [35].

TZP-102

A phase IIa study demonstrated that TZP-102 reduced abdominal symptoms without significantly improving gastric emptying in patients with diabetic gastroparesis, compared with placebo [37]. Subsequently, phase IIb trials failed to show a significant difference in improving gastrointestinal mobility between TZP -102 and placebo. No developments regarding TZP-102 have been updated recently, because Ocera Therapeutics merged with Tranzyme Pharmaceutical, the maker of TZP-102, in 2013.

Indication of body composition: Ibutamoren, Tesamorelin, Capromoreline, Anamoreline, and Macimoreline

Ibutamoren

In the stimulating scenario of GH production, the long-term safety of treatment with growth hormone (GH) is an area of much debate. Healthy elderly people who took the MK-677 mimetic experienced a sustained increase in the amplitude of pulsatile GH and IGF-I secretion to the levels seen in young adults [38].

GH reduces abdominal visceral fat (GVA) in GH deficient and obese adults, postmenopausal women, but not in normal elderly people. Despite the increased GH levels, MK-677 did not affect GAV, perhaps because its combined orexigenic and adipogenic effects neutralized the lipolytic effects of the GH increase. Finally, although MK-677 did not reduce GVA, it did reduce LDL levels in 12 months and the unobserved effect on GH in normal elderly people [38].

In a randomized clinical trial, ibutamoren for 12 months was well tolerated and increased GH secretion and fat-free mass, but not muscle strength in healthy elderly people. However, development was halted because ibutamoren was associated with the risk of heart failure in a randomized study to examine safety and efficacy in patients with hip fractures [38].

Tesamorelin

Several randomized clinical trials have shown the beneficial effects of tesamorelin on impaired body composition in patients with HIV-associated lipodystrophy [39-42]. A meta-analysis including four clinical studies also revealed that tesamorelin decreased visceral fat and increased lean body mass. As a result, the FDA approved tesamorelin (Egrifta®) as the first-line treatment for reducing excess abdominal fat in HIV-infected patients with lipodystrophy.

Capromorelin

A Phase II clinical trial investigated the effects of capromorelin on body composition and functional performance in healthy elderly people. At 12 months, capromorelin significantly increased lean body mass and the ability to climb stairs compared to placebo. However, this study was terminated early because results at 12 months were not considered a continuation of this study [43]. As the aging process is not considered a pathological condition by the FDA, capromorelin must offer excellent results, as a survival benefit in this case. population or be applied to other clinical indications. Capromorelin has so far only been approved by the FDA as a short-term therapeutic option for improving appetite in anorexic dogs.

Anamorelin

Two-phase III, double-blind trials (ROMANA 1, NCT01387269, n = 484; ROMANA 2, NCT01387282, n = 495) evaluated the efficacy and safety of anamorelin 100 mg in patients with incalculable stage III / IV lung cancer and cachexia defined as [?]5% weight loss in the last 6 months or a body mass index <20 kg / m2. In both studies, anamorelin increased lean body mass compared to placebo (ROMANA 1: 1.10 kg for anamorelin, -0.44 kg for placebo; ROMANA 2: 0.75 kg for anamorelin, 0.96 kg for placebo; P <0.0001 for both), but did not significantly improve handgrip strength.56 Subsequently, an extension study, ROMANA3 (NCT01395914), involving 513 patients with ROMANA1 and ROMANA2 NSCLC, assessed the efficacy and safety of anamorelin for another 12 weeks. As in previous studies, anamorelin has been associated with a favorable safety profile and increased body weight, but not muscle strength [44]. Anamorelin showed similar results in a clinical trial that included patients with NSCLC-induced cachexia in Japan [Clinical trial record: JapicCTI-111415 (Japan Pharmaceutical Information Center Clinical Trials Although several clinical studies have shown that anamorelin increased muscle mass, but not muscle strength, anamorelin did not receive approval in 2017, despite promising results in clinical studies, because increasing muscle mass without a significant increase in muscle strength was not considered acceptable.

Table 1. Current status of the main GHS found.

SUBSTANCE	STATUS	DATE	CLINICAL INDICATIONS AND DESCRIPTIONS
Sermorelin	FDA approved and discontinued	July, 2008	IN SEPTEMBER 1997, SERMORELIN WAS APPROVED FOR THE TREATMENT OF GROWTH HORMONE DEFICIENCY IN CHILDREN
Examorelin	Interrupted		
Tabimorelin	Interrupted	AT	IT SEEMS INTERRUPTED.
Pralmorelin (i.v.)	Approved in Japan	October, 2004	DIAGNOSIS OF GROWTH HORMONE DEFICIENCY IN ADULTS AND CHILDREN (> 4 YEARS).
Ipamorelin	Interrupted		
Ulimorelin	Active	March, 2017	EVALUATING THE EFFECT OF ULIMORELIN IN PATIENTS WITH INTOLERANCE OF ENTERAL FEEDING
Relamorelin	Currently evaluated by the FDA	October, 2016	TREATMENT OF DIABETIC GASTROPARESIS.
TZP-102	Active	2013	FDA GIVES TZP-102 A QUICK DESIGNATION FOR TREATMENT OF DIABETIC GASTROPARESIS IN 2009.
Tesamorelin	FDA approved	November, 2010	REDUCTION OF EXCESS ABDOMINAL FAT IN HIV INFECTED PATIENTS WITH LIPODYSTROPHY.
Capromorelin (oral)	FDA approved	June, 2016	APPETITE STIMULATION IN DOGS WITH DECREASED APPETITE.
Anamorelin	Requested for approval at EMA	November, 2015	CACHEXIA ASSOCIATED WITH NSCLC.

SUBSTANCE	STATUS	DATE	CLINICAL INDICATIONS AND DESCRIPTIONS
Macimorelin	Requested for FDA approval	February, 2017	DIAGNOSIS OF GROWTH HORMONE DEFICIENCY IN ADULTS.

SELECTIVE MODULATORS OF ANDROGENIC RECEPTORS - SARM

Scientific clinical results in the last 10 years

In the past two decades, scientists' efforts have focused on the discovery and biological characterization of new tissue-specific SARM to promote the beneficial effects of androgens with greatly reduced undesirable side effects. In this regard, numerous studies with SARM of different structures have been reported, as shown in Table 2.

Table 2. Different SARM structures [45-48].

- SARM with central arylpropionamide structure, such as S-1, S-4 (andarina), S-9, S-22
- SARM with central phenyl oxadiazole structure, such as RAD140
- SARM with central quinolinone structure, such as LGD-2226, LGD-2941, LGD-3303
- SARM with tetrahydroquinolinone core structure, such as S-40503, S-101479, S-49288
- SARM with indole core structure, such as RAD35010, Ly2452473

Despite evidenced clinical and preclinical studies, no SARM has yet received full clinical approval. However, the enormous anabolic properties of SARM muscles and bones give rise to potential misuse in sports, as has been recognized by the World Anti-Doping Agency (WADA), which has included SARM in the banned list released annually since 2008 (class S1.2, other anabolic agents) [45].

Due to its considerable variety of central chemical structure and the display of substantially different physical and chemical properties, the generation of SARM data related to ionization and dissociation of substances under analytical conditions commonly used in doping control laboratories is crucial for routine testing of sports drugs. Therefore, drug candidates have been subjected to electrospray ionization, high-resolution mass spectrometry, and electron ionization, to reveal structural information that supports the development of test methods and metabolism studies [46].

In this context, LGD-4033 (also known as VK5211, Ligandrol or Anabolicum) (4 - ((R)-2-((R)-2,2,2-trifluoro-1-hydroxyethy1) pyrrolidine-1-y1) -2-trifluoro-methyl) benzonitrile) is a SARM with a central structure of pyrrolidinyl-benzonitrile [47]. A study in young, healthy men proved that LGD-4033 is safe, well-tolerated, has a favorable pharmacokinetic profile with a prolonged elimination half-life (24-36 hours), in addition to showing increased lean body mass. Longer randomized studies should assess its effectiveness in improving physical function and health benefits. Although its use is not officially approved and is not yet manufactured by a pharmaceutical company, many websites make LGD-4033 widely available and studies have reported its detection in black market products [47].

A study of LGD-4033 metabolism in human urine, as well as in a doping control sample from a human athlete, has been reported. The metabolites of microsomes by the human liver, as well as electrochemical conversion metabolites / microbial degradation of LGD-4033 have also been described [47].

GlaxoSmithKline (GSK) 2881078 is a selective non-steroidal SARM modulator under investigation by GSK for the treatment of reduced mobility and other functional limitations in men and women with muscle

weakness associated with chronic and acute diseases [48]. Thus, in a human study, we report the safety, tolerability, pharmacokinetics, and pharmacodynamics of SARM GSK2881078. In part A, healthy young men (n = 10) received a single dose of the study drug (0 mg, 0.05 mg, 0.1 mg, 0.2 mg gsk2881078 or corresponding placebo). In part b, the cohorts of repeated doses in men (n = 65) were 0.05 mg, 0.2 mg and 0.08 mg, 0.24 mg, 0.48 mg, 0.75 mg or placebo; in women (n = 24) it was 0.24 mg, 0.35 mg or placebo (7 days for 0.5 mg, 14 days for other doses). Pharmacokinetic analysis showed dose-proportional increases in exposure and a long half-life> 100 h. There were no significant effects on vital signs, electrocardiograms, cardiac telemetry, or standard clinical laboratory studies. A dose-response effect was observed in the reduction of high-density lipoprotein and sex hormone-binding globulin. In women with 0.35 mg, the differences from placebo were -0.518 (95% confidence interval: -0.703, -0.334) mmol l-1 and -39.1 (-48.5, -29.7) nmol l-1, respectively. Women showed greater sensitivity to these parameters at lower doses than men. Adverse drug-related events were mild. One woman developed a rash and was removed. Two men had elevated creatine phosphokinase after physical exertion during follow-up. Therefore, these data demonstrated pharmacodynamic effects with acceptable tolerability and support an additional clinical assessment of this SARM [48].

Still, another phase 1b study aimed at exploring, over a range of doses, the pharmacokinetic relationship and more safety and tolerability data for gsk2881078 [49]. This study also evaluated the effects of cyp3a4 inhibition on the pharmacokinetics of gsk2881078. This study followed a randomized, placebo-controlled, parallel-group, repeated dose, and dose escalation model in older healthy men and postmenopausal women. Three male and three female cohorts were studied. Dosing at each dose level was twice daily for the first 3 days, followed by once daily for up to 53 days. Repeated x-ray absorptiometry and magnetic resonance imaging were performed in the cross-section of the thigh. The effect of cyp3a4 inhibition on gsk2881078 was evaluated in a separate cohort. The gsk2881078 was generally well tolerated and no serious adverse events were reported. Compared with the placebo, there was a greater accumulation of lean mass with all dose levels of gsk2881078. Women exhibited a greater response at lower doses than men. Transient elevations of alanine aminotransferase were observed. The effect of cyp3a4 inhibition on gks2881078 is likely to have no clinical significance. Therefore, gsk2881078 produced dose-dependent increases in lean mass, with evidence of greater sensitivity in women. The compound was well tolerated [49].

Also, the assembly of inflammasomes after infection or injury leads to the release of interleukin-1β (IL-1β) and pyroptosis. After activation of the inflammasome, the pyroptosis cells either enter a hyperactive state defined by the secretion of IL-1β without cell death. The removal of the toll-il-1r SARM protein from macrophages decouples the release of inflammasome-dependent cytokines and pyroptosis, in which cells exhibit increased production of IL-1β, but reduce pyroptosis in the same way. The increase in sarm in the cells caused less release of IL-1β and pyroptosis. SARM suppressed IL-1β by directly restricting the nlrp3 inflammasome and, therefore, caspase-1 activation [50].

A steroid compound was recently detected as (17α, 20e) -17.20 - [(1-methoxyethylidene) bis (oxy)] - 3-oxo-19-norpregna-4,20- diene-21-carboxylic acid methyl ester (yk11). This compound is described as having selective properties of androgen receptor modulators and myostatin inhibitor. As yk11 is an experimental drug candidate and an unapproved substance for humans, scientific data on its metabolism is scarce. Due to its steroid backbone and the undisputably labile derived orthoester portion, positioned in the d ring, substantial *in vivo*metabolic conversion was anticipated [51].

Also, RA has attracted attention in the treatment of breast cancer. Due to the undesirable side effects of ar agonists, attempts have been made to develop selective RA modulators. Thus, one of these compounds is cl-4as-1. three different breast cancer cell lines were used, namely, mcf-7 luminal cells, mda-mb-453 apocrine molecular cells, and triple-negative basal cells, mda-mb-231. The high and significant agreement was found between dihydrotestosterone (DHT) and cl-4as-1 in the regulation of gene expression in mda-mb-453 cells. however, some differences were observed, including the expression of RA, which was regulated by DHT, but not by cl-4as-1. Also, DHT and cl-4as-1 caused a similar morphological change and reorganization of the actin structure of mda-mb-453 cells into a mesenchymal phenotype. Treatment of cells with dht resulted in the induction of the proliferation of mcf-7 and mda-mb-453 cells, but no effect was observed on the growth

of mda-mb-231 cells. On the other hand, increasing doses of cl-4as-1 resulted in a dose-dependent inhibition of the growth of the three cell lines. This inhibition was the result of the induction of apoptosis by which cl-4as-1 caused a block in the entry of cells in the s phase, followed by DNA degradation. Therefore, these results indicate that, although cl-4as-1 has characteristics of the classic RA agonist, it has different properties that may make it useful in the treatment of breast cancer [52].

Also, a report described the discovery of RAD140, a potent non-steroidal selective modulator, orally bioavailable, non-selective steroid for RA. The characterization of RAD140 in several preclinical models of anabolic androgen action is also described. RAD140 has excellent pharmacokinetics and is a potent anabolic also in non-human primates. The general preclinical profile of RAD140 completed preclinical toxicology in rats and monkeys. At the moment, RAD140 is being prepared for phase 1 clinical studies in patients suffering from weight loss due to cancer cachexia [53].

In this sense, loss of muscle mass in cancer is a common and often hidden condition that can occur before obvious signs of weight loss and before a clinical diagnosis of cachexia can be made. Muscle wastage in cancer is an important and independent predictor of progressive functional impairment, decreased quality of life and increased mortality. Although several therapeutic agents are currently under development to treat muscle wasting or cachexia in cancer, most of these agents do not directly inhibit muscle wasting. Thus, SARMs have the potential to increase lean body mass and, therefore, muscle mass, without the undesirable side effects seen with traditional anabolic agents [54].

Thus, Enobosarm, a non-steroid SARM, is an agent in the clinical development for preventing and treating muscle wasting in cancer patients (phase 1 and 2 trials). Also, a phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational trial was designed to evaluate the effectiveness of Enobosarm in preventing and treating muscle wasting in individuals who initiate first-line chemotherapy for non-chemotherapy. little. In each study, subjects will receive either placebo (n = 150) or Enobosarm 3 mg (n = 150) orally once daily for 147 days. Physical function, assessed as the power to climb stairs, and lean mass assessed by dual-energy x-ray absorptiometry, are the end points of effectiveness in both tests evaluated on the day. Based on extensive comments from the Food and Drug Administration (FDA), an individual should experience a 10% improvement in physical function compared to the baseline. To meet the definition of response in lean mass, a subject must have demonstrated no loss of lean mass compared to the baseline. Secondary end points include the durability of the assessed response. The efficacy parameters are the result of this feedback and discussion of the threshold for clinical benefit in patients at risk of muscle loss. The full results of these studies will be published shortly [54].

Also, a selective non-steroidal modulator named ly305 has been identified, which is bioavailable through a transdermal route of administration while being highly eliminated by hepatic metabolism to limit the exposure of parent compounds in the liver. The selection of this compound and its transdermal formulation was based on the optimization of skin absorption properties using in vitro and *in vivo* skin models. This molecule is an agonist of the perineal muscle and is a weak partial agonist of androgenic tissues, such as the prostate. When ly305 was tested on animal models of skeletal atrophy, it restored skeletal muscle mass through accelerated repair. In a model of bone fracture, ly305 remained osteoprotective in the regenerating tissue and without deleterious effects. In a small cohort of healthy volunteers, the safety and tolerability of ly305 was assessed when administered transdermally. Ly305 showed a dose-dependent increase in serum exposure and was well tolerated with minimal adverse effects. Notably, there were no statistically significant changes in hematocrit or HDL after the 4-week treatment period. Collectively, ly305 represents the first of its kind to develop a non-steroidal transdermal SARM with unique properties that may find clinical utility [55].

The gtx-024 (Enobosarm) is the first selective modulator of androgen receptors of the class, being developed for several indications in oncology. Pre-clinical studies of gtx-024 supported the evaluation of several potential drug interactions in a clinical setting. A series of open phase 1 drug interaction studies was designed to interrogate possible interactions with a cyp3a4 inhibitor (itraconazole), a cyp3a4 inducer (rifampicin), a pan-ugt inhibitor (probenid), a cyp2c9 substrate (celecoxib)) and a bcrp substrate (rosuvastatin). The

plasma pharmacokinetics of gtx-024, its main metabolite (glucuronide gtx-024) and each substrate were characterized in detail. Administration of itraconazole did not affect the pharmacokinetics of gtx-024. Likewise, the administration of gtx-024 did not significantly alter the pharmacokinetics of celecoxib or rosuvastatin. Administration of rifampicin had the greatest impact on the pharmacokinetics of gtx-024 of any co-administered agent and reduced the maximum plasma concentration by 23% and the area under the curve by 43%. Probenecid had a complex interaction with gtx-024, so plasma levels of gtx-024 and glucuronide gtx-024 were increased by coadministration of the ugt inhibitor (50 and 112%, respectively). Overall, gtx-024 was well tolerated and has very little risk of generating clinically relevant drug interactions [56].

ANTAGONISTS

Loss of skeletal muscle mass and strength is a central feature of traumatic injuries and degenerative myopathies. Unfortunately, pharmacological interventions often fail to stem the long-term decline in quality of life. REV-ERB-mediated reduced gene suppression in cultured c2c12 myoblasts has been shown to stimulate myoblast differentiation. However, the mechanisms that allow REV-ERB to pleiotropically inhibit muscle differentiation are not well known. Thus, a study elucidated the role of REV-ERB in regulating muscle differentiation and regeneration *in vivo*. The REV-ERB α/β regulation mechanism for muscle differentiation and regeneration was analyzed. Myoblast analysis showed that REV-ERB α did not transcriptionally regulate muscle differentiation through cognate elements REV-ERB/ror-response, but through a possible interaction with the regulator of nf-y cell fate in ccaat motifs. Muscle differentiation is stimulated by the release of REV-ERB from CCAAT motifs in the elements promoting and enhancing various myogenic proteins. Therefore, the interruption of REV-ERB activity in the injured muscle accelerates regenerative muscle repair/differentiation through the transcriptional detoxification of myogenic programs. Thus, REV-ERB can be a potent therapeutic target for a multitude of muscle disorders [57].

In previous investigations, we have reported that activation of the β/δ receptor activated by the peroxisome proliferator by gw501516 inhibits proliferation and promotes apoptosis in the undifferentiated cells of c666-1 nasopharyngeal carcinoma (NPC) modulating the caspase-dependent apoptotic pathway. Thus, a study explored the mechanism by which gw501516 induces apoptosis through the expression of the microwave (mirna). Among the mirnas analyzed involved in regulating the expression of the anti-apoptotic protein bcl-2, mir-206 increased significantly and specifically by gw501516 in c666-1 cells, both in vitro and in xenograft samples *in vivo* . The induction in mir-206 expression caused by gw501516 was able to be antagonized by the antagonist gsk3787 of pparβ/δ and by the dorsomorphine antagonist of ampk in cells c666-1. Suppression of gw501516 in the growth and apoptosis of c666-1 cells has been found to depend on the presence of mir-206 [58].

The overexpression of mir-206 resulted in suppressed proliferation and the ability to form colonies, in addition to triggering increased apoptosis in c666-1 cells in a caspase-dependent manner. the expression of cleaved caspase 3 and caspase 9, and the ratio of bax to bcl-2 were increased notably by mir-206. Current data has shown that mir-206 plays a critical role in the direct promotion effect of gw501516-induced apoptosis in c666-1 cells. Also, the emphasized tumor-suppressing role of mir-206 in c666-1 cells indicates that it has the potential to provide a new therapeutic approach [58].

CONCLUSION

Several clinical trials have been conducted and completed to assess the safety and efficacy of GHS for the diagnosis and/or treatment of GH deficiency. Over the past two decades, scientists' efforts have focused on the discovery and biological characterization of new tissue-specific SARM to promote the beneficial effects of androgens with greatly reduced undesirable side effects. In this regard, numerous studies with SARM of different structures have been reported. Despite evidenced clinical and preclinical studies, no SARM has yet received full clinical approval.

Conflict of interest

The authors declare no conflict of interest.

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