Update on the Role of Actovegin in Musculoskeletal Medicine: A Review of the Past 10 Years

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Abstract

Background: Actovegin is a biological drug with a controversial history of use in the treatment of sports injuries during the past 60 years. Particular concerns have been raised about its ergogenic potential to enhance performance, but some of these have been based on little more than anecdote. **Objectives:** In this article, we review the most recent scientific evidence to determine the clinical efficacy, safety profile, and legal status of Actovegin. **Methods:** We considered all studies directly commenting on experience with Actovegin use as the primary intervention within the past 10 years. Outcomes included mechanisms of action, clinical efficacy in enhancing muscle repair, any report of safety issues, and any evidence for ergogenic effect. **Results:** Our database search returned 212 articles, abstracts were screened, and after inclusion/exclusion criteria were applied, 25 articles were considered: Publications included 11 primary research articles (7 in vitro studies and 4 clinical trials), 8 review articles, 5 editorials, and a single case report. **Conclusions:** Current literature is still yet to define the active compound(s) of Actovegin, but suggests that it shows antioxidant and antiapoptotic properties, and may also upregulate macrophage responses central to muscle repair. Clinical efficacy was supported by one new original research article, and the use of Actovegin to treat muscle injuries remains safe and supported. Two articles argued the ergogenic effect of Actovegin, but in vitro findings did not to translate to the outcomes of a clinical trial. An adequate and meaningful scientific approach remains difficult in a field where there is immense pressure to deliver cutting-edge therapies.

Key Words: Actovegin, biological drug, muscle, musculoskeletal, sports injury

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INTRODUCTION

Actovegin is a biological drug produced by Nycomed GmbH, Linz, Austria, which in 2015 was taken over by Takeda Pharmaceutical Ltd, Japan.[1] It has a 60-year history of safe use as an injection therapy for sports muscle injuries. The use of Actovegin in training regimes by high-profile athletes has led to the anecdotal opinion that the blood product is ergogenic, enhancing athlete performance. In vitro studies have suggested that Actovegin improves the efficacy of energy balance in cells during postischemic metabolic events, while also having membrane stabilizing effects to interrupt the processes of oxidative stress and cell death. A recent in vitro cell injury model showed that Actovegin improved intrinsic mitochondrial respiratory capacity in injured human skeletal muscle fibers; the group concluded that their findings supported and explained the reported ergogenic properties.[2] However, results of a previous clinical trial have shown that Actovegin has no effect on peak aerobic capacity in humans in vivo.[3] The conflicting literature and widespread anecdotal opinion stemming from unpublished case series has led to Actovegin receiving a great deal of media attention. Conflicting opinion often arises due to a weak scientific base and the pressure to deliver cutting-edge treatment in the field of sports medicine, an aspect we have highlighted in our last review of the status of Actovegin.[4] This article therefore aims to recap some of the outstanding issues surrounding Actovegin and, through review of the most recent scientific literature, further addresses these areas.

OBJECTIVES

To address the outstanding issues of our last review based on recent literature of the past 10 years, the aims of this article are as follows:

1. To review preclinical evidence, specifically to identify any active components of Actovegin or investigating its role in the modulation of inflammatory processes;
2. To evaluate any improvement to the limited evidence base of the role of Actovegin in treating muscular injuries and to monitor its continued safe profile; and
3. To review the effect of Actovegin on ergogenic potential and its subsequent licensing status.

METHODS

We considered all studies directly commenting on experience with Actovegin use as the primary intervention. Original research conducted within the past 10 years was

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included. This mainly included in vitro study, case/case–control study, and review articles. Review articles were included and references read to ensure no primary articles were missed. All participants and models for Actovegin use were considered with the primary indication being a skeletal muscle injury.

Studies considering interventions of similar blood product derivatives, platelet-rich plasma (PRP), and autologous conditioned serum (ACS), but not specifically Actovegin as either the primary or control intervention, were excluded.

Outcomes included evidence for mechanisms of action, clinical efficacy in enhancing muscle repair, any report of safety concerns, and any evidence for ergogenic effect.

We searched PubMed, MEDLINE (Ovid), and Cochrane databases for all articles published since January 1, 2007 with the term "Actovegin." To obtain the most recent data, this was initially a 5-year search but due to the paucity of literature on Actovegin, this was extended to 10 years. This allowed for the greatest amount of up-to-date literature to be assessed and potentially included. Google Scholar was further searched for the term Actovegin with the key terms "Sports Injury," "Injection Therapy", and "Muscle." No other search restrictions were applied. We also searched for the current controlled trials at www.controlled-trials.com (Accessed July 2017).

The results of the search and exclusion criteria at each stage are included in Figure 1.

RESULTS AND DISCUSSION

The search process and results are documented in Figure 1. In total, 25 studies were included spanning the past 10 years; 2008 (1), 2009 (2), 2010 (3), 2011 (5), 2012 (4), 2014 (4), 2015 (1), 2016 (4), and 2017 (1). In total, the studies included 11 primary research articles, 8 review articles, 5 editorials, and 1 case report. Of the primary research articles, 4 were clinical and 7 were in vitro studies.

Articles have been grouped based on the issue surrounding Actovegin that they aim to address. Of importance, the only 2 original research articles to be performed within the past 5 years address the highly controversial area surrounding the speculated ergogenic potential of Actovegin.

Ergogenic Potential and Legality

- To review the effect of Actovegin on ergogenic potential and its subsequent licensing status.

Actovegin has received a great deal of media attention in the field of Sports Medicine, largely based on anecdotal comments suggesting that injection therapy is ergogenic and has potential to enhance athletic performance. Our review returned 4 original articles, 2 researching the ergogenic effect of Actovegin and 2 articles commenting on the legal status of the biological drug. Both articles commenting on the legal status cite the same original research article; therefore, the original research article is included in Table 1, which summarizes the original research cited in this section.

Tsitsimpikou et al[5,6] reported in 2 articles on the medications taken by athletes at both the 2004 Olympic and Paralympic Games, commenting on the legal status of Actovegin as a result of these global competitions. Actovegin was banned as an ergogenic blood doping agent by the IOC in December 2000, after they noted its prolific use during the Sydney Olympics. However, this ban was lifted 2 months later because no definitive scientific evidence could be provided to support the ban. The only study cited by the IOC and Tsitsimpikou et al was an article published by Ziegler et al,[7] which looked at muscle strength improvements as part of a secondary outcome measure in treatment of diabetic neuropathy showing no effect. Owing to the original evidence behind these comments, this article is included in Table 1.

Lee et al[3] (2012) performed a blinded, crossover peak aerobic capacity study in healthy human participants. The participants had a mean age, height and weight of 24 years, 1.76 cm, and 80.1 kg, respectively. Participants performed 3 exhaustive arm crank ergometry tests, before and twice after being infused with 40 mL (maximal dose) of Actovegin. Through thorough outcome testing, it was demonstrated that Actovegin had no ergogenic effect on peak power, peak physiological response, blood glucose or lactate concentration, exercise efficiency, or rate of $\dot{V}O_2$ gain. The findings of this exhaustive, clinical, upper-body test suggests that Actovegin has no effect on functional capacity and, therefore, the drug should not be viewed as being ergogenic.

Søndergård et al[2] performed an in vitro cell membrane study measuring mitochondrial respiratory capacity in

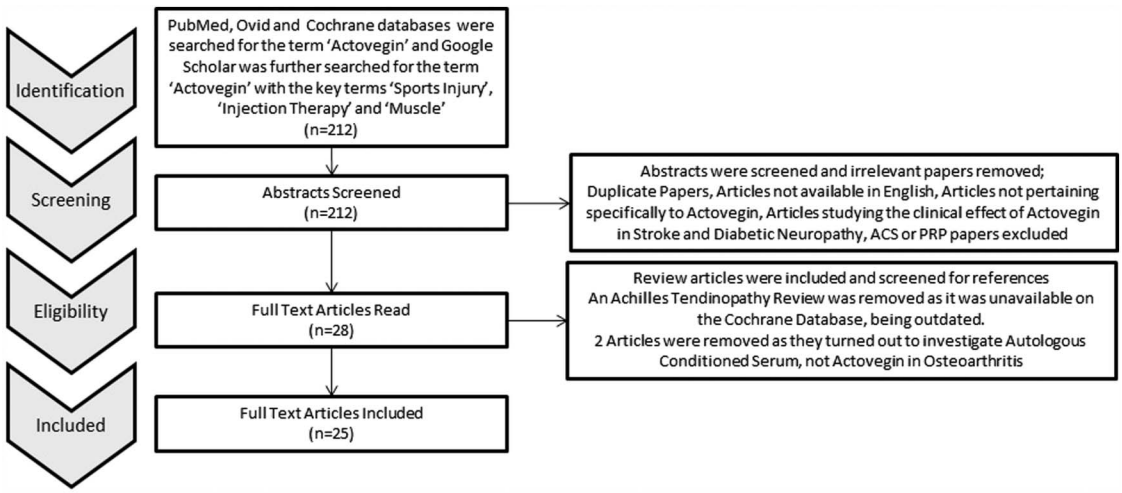

Figure 1.
Flow Diagram of Search Strategies.

TABLE 1. Outlining the Key Articles Investigating Ergogenic Potential

Study	Type of Study	Participants	Methods	Outcome Measures	Results	Limitations
Ziegler et al, 2009[7] (set superior) cited by Tsitsimpikou et al, 2009[5,6]	Clinical trial	567 patients with type 2 diabetes	20 intravenous infusions of Actovegin 2000 mg/d (n = 281) or placebo (n = 286)	Neuropathy Impairment Score of the Lower Limbs (NIS-LL) component. Composing of muscle strength (0 = normal, 4 = paralyzed) and sensory nerve function.	NIS-LL significantly improved with Actovegin therapy ($P = 0.08$) because of significantly improved sensory function ($P = 0.005$) but not muscle strength ($P = 0.731$) or muscle reflexes ($P = 0.571$).	Muscle improvement was studied as a partial component of a secondary outcome parameter.
Lee et al, 2011	Clinical Trial	8 male participants, mean (SD) of 24 (7) yrs, stature of 1.76 (0.07) m, and body mass of 80.1 (9.1) kg.	40 mL of Actovegin injection or saline placebo. 3 exhaustive arm crank ergometry tests.	Peak power, peak physiological responses, blood glucose and lactate concentrations, exercise efficiency, $\dot{V}o_2$ gain and respiratory compensation point (RCP). Outcomes measured before and 2 h after injection.	Minimal effect was noted between Placebo and Actovegin within peak power (0.8 ± 3.2) and RCP (2.5 ± 4.7 W). Blood glucose and lactate did not differ between the 3 trials.	Small sample size on amateur level athlete only. Possible limited transferability of results to elite-trained subjects.
Sondergaard et al, 2016	In vitro	Skeletal muscle biopsies taken from 8 overweight untrained subjects, mean (SD) age 47 (5) yrs, body mass index 34 (2) kg/m^2, fat percentage 37 (5) % and $\dot{V}o_2$ max 27 (3) ml·min^{-1}·kg^{-1}.	Biopsies split into 3, control solution of BIOPS and Saponin (50 μg/mL), 10 μL/mL Actovegin or 50 μL/mL Actovegin. Actovegin concentration 40 mg/mL.	Cell injury study on oxidative phosphorylation capacity (OXPHOS) for complex I and II-linked substrates. Respiratory capacity of the electron transfer system (RC-ETS), Vmax and Km.	Complex I-linked substrate OXPHOS capacity increased in a concentration-dependent manner (19 ± 3, 31 ± 4, and 45 ± 4 pmol·mg^{-1}·s^{-1}). Max OXPHOS capacity of complex I and II increase with high dose Actovegin (62 ± 6 and 77 ± 6 pmol·mg^{-1}·s^{-1}, $P <$ 0.05). RC-ETS, Vmax and Km also increased in a concentration-dependent manner. Actovegin has a marked effect on intrinsic mitochondrial capacity on injured cells.	A lack of comparison between the observed increased mitochondrial respiratory capacity and exercise capacity. The effect of Actovegin was tested in permeabilized muscle fibers, but whether Actovegin in vivo actually can cross the cell membrane and exerts its effect on the mitochondria is not known. The use of Saponin a cytotoxic drug could lead this study to be viewed as a cell injury study.

permeabilized human skeletal muscle fibers exposed to Actovegin therapy. They suggested that Actovegin increased mitochondrial oxidative phosphorylation capacity, Vmax, and Km of human skeletal muscle in a dose-dependent manner. The authors noted that normally, increased mitochondrial respiratory capacity through training is due to an increase in mitochondrial number, rather than an improvement of their intrinsic capacity. The authors went on to speculate that these findings could translate to in vivo effects of enhancing human performance. It is important to note that the treatment of muscle fiberswith Saponin in this experiment. Saponin is used as a cytotoxic chemotherapy drug with major reported side effects, stimulating the Th1 immune response and production of natural killer cells leading to hemolysis of cells. Saponin has been used in clinical trials but was found to have toxicity issues associated with sterol complexation. However, the use of Saponin is not necessarily a limitation to the study by Søndergård et al. The pretreatment of human skeletal muscle with Saponin leads us to view the study as an in vitro cell membrane injury study, similar to the effects observed in grades I or II muscle tears, certainly not to be interpreted as a performance-based study. The aforementioned study by Lee et al[3] demonstrated that the speculative extrapolations made by Søndergård et al do not carry through to affect in vivo human peak aerobic capacity. The study does, however, provide evidence behind the protective metabolic effects of Actovegin in hypoxic cell injury and supports its clinical use as an injection therapy for sports muscle injuries.

Currently, intramuscular use of Actovegin is permitted both in or out of competition for any given sport, according to the latest search (March, 2017) in the Global Drug Reference Online, which is approved by United Kingdom. Anti-Doping, the Canadian Centre for Ethics in Sport, the U.S. Anti-Doping Agency, and WADA.[8,9] However, it is stated that the intravenous infusion or injection of more than 50 mL every 6 hours of any substance is prohibited, unless it is received during a hospital admission, a surgical procedure, or a clinical investigation, even if the substance itself is not prohibited.[9] The results from this literature review suggest that care must be taken when extrapolating in vitro results, as they may not necessarily translate to changes in human performance. We would also advocate that the current stance taken by anti–doping agencies is correct, given the scientific evidence available.

Preclinical Evidence and Mechanism of Action

- To review preclinical evidence, specifically to identify any active components of Actovegin or investigating its role in the modulation of inflammatory processes.

Actovegin has several active components that have yet to be identified. Possible mechanisms include the action of inositol phosphate oligosaccharides (IPOs) and insulin-like effect during hypoxic injury, with a recent review beginning to shed light on the anti-inflammatory role. Our search returned 6 primary research articles and 2 review articles investigating possible mechanisms. Table 2 summarizes the articles included in this section.

Astashkin et al concluded that Actovegin protects cells of various organs and tissues by reducing the level of reactive oxygen species (ROS) produced as a result of ischemia and inflammation.[10] They reported that Actovegin inhibits spontaneous and induced formation of ROS generated by blood phagocytes of patients with heart failure. It was also shown that Actovegin suppresses hydrogen peroxide–induced necrosis of human SK-N-SH neuroblastoma cells. This suppression of ROS produced during an inflammatory process may be extrapolated to the protective effects of Actovegin injection therapy viewed clinically in muscle tears.

Yurinskaya et al[11] also studied the effect of Actovegin on hydrogen peroxide–induced apoptosis of SK-N-SH neuroblastoma cells. Their study, however, showed that Actovegin is also reducing mitogen-activating protein kinase (p38MAPK) and phosphatidylinositol 3-kinase (PI-3K) pathway activity.[11] It is widely accepted that the p38MAPK and PI-3K signaling pathways are involved in cell death by apoptosis. Therefore, the inhibition of apoptosis during ischemic cell injury seen in muscle tears may preserve cell viability leading to the observed clinical effect in promoting and enhancing muscle repair.

Lee et al[12] described the potential role of Actovegin in upregulating $CD68^+$ macrophages in a preliminary, laboratory-based gene expression report. Macrophages have been suggested to have an active role in promoting muscle regeneration. The $CD68^+$ macrophages are not only involved in phagocytosis in the initial 24 hours after injury, but also act to secrete inflammatory cytokines such as tumor necrosis factor–alpha and interleukin (IL)-1 that recruit $CD163^+$ macrophages, which display anti-inflammatory properties by utilizing IL-10 to terminate inflammation.

Machicao et al[13] reviewed the mechanisms of action of Actovegin. Within this article, they report the results of an in vitro study investigating the effect of Actovegin on the nuclear factor (NF)-kB pathway, conducted by Hundsberger and Pfluger (Unpublished Observations). Embryonic kidney cell lines showed activation of NF-kB reporter gene expression in a dose-dependent response to Actovegin treatment. NF-kB has been shown to directly regulate MyoD, cyclin D1, and MuRF1 in skeletal muscle disease and is a major pleiotropic transcription factor for modulating inflammation, proliferation, and cell survival responses. Machiacao et al also conducted a review of slightly older literature, highlighting the potential that Actovegin acts to improve metabolic balance by enhancing glucose and oxygen uptake in conditions of ischemia. They further highlighted specific antioxidative and antiapoptotic mechanisms confirmed in the aforementioned studies by Atashkin et al[10] and Yurinskaya et al,[11] respectively.

Gulevsky et al[14] considered the influence of Actovegin on the proliferative activity and mitotic regimes of various cell lines. Both cell lines showed an increase in proliferative activity of 21% and 36%, respectively, in response to 0.14% Actovegin in combination with 2% cattle blood serum. This finding suggested that Actovegin modulated the bioenergetic state of cells, possibly due to increase oxygen and glucose consumption in an insulin-like effect, something echoed by Buchmayer et al[15] and Lee et al.[4] Furthermore, Actovegin was shown to stimulate mitotic activity by 36% within 24 hours, suggesting that it may have growth factor–like effects, something previously demonstrated on fibroblast and endothelial cell growth factors highlighted in the review by Lee et al.[4,14]

In their second article on Actovegin, Gulevsky et al[16] looked at the effect of Actovegin and low-molecular-weight cattle cord blood on the activity of frozen-thawed leukocyte activity. The phagocytic index increased 1.26-fold after treatment with 1.5 mg/mL of Actovegin, suggesting that Actovegin significantly activated the engulfing and digestive functions of neutrophils.

Both Buchmayer et al[15] and Lee et al[4] gave reviews of the pharmacodynamic actions and the benefits of Actovegin in a clinical setting. Both cite the important role of IPO, a putative ingredient of Actovegin that stimulate glucose transporter activity promoting glucose uptake by cells, contributing to up to 50% of the maximum insulin effect.

The most up-to-date literature, therefore, suggests that Actovegin exhibits antioxidant and antiapoptotic properties. Furthermore, Actovegin may play a role in the upregulation of macrophage responses central to muscle repair. Future research should consider this role using larger studies, in vivo and begin to identify active ingredients responsible for influencing such regulatory bodies.

Clinical Evidence and Safety Profile

- To evaluate any improvement to the limited evidence base of the role of Actovegin in treating muscular injuries and to monitor its continued safe profile.

This review of literature returned several other review articles, 3 looked at the etiology and treatment options of hamstring muscle injuries (Hamilton, Reurink et al, and Linklater et al), whereas 2 others looked more widely at regenerative medicine and injection therapies (Laupheimer et al, Smith, and Segal).[17–22] All articles cited the same evidence when commenting on the status of Actovegin, circulating back to the initial work by Pfister and Koller. These workers performed a partially blinded case–control study of 103 patients, at 3 months follow-up; they found an improvement in recovery time of 2.8 weeks in the Actovegin-treated group.[23] The study by Wright-Carpenter et al, examined the effect of ACS on muscle injury compared with an Actovegin/Traumeel regime. Although this article was frequently cited, it should not be viewed as new evidence as it merely referred to the previous work by Pfister and Koller.[24] All reviews concluded that this evidence was outdated and insufficient to advocate the use of Actovegin as a modern injection therapy for muscle injury. Table 3 compares the 2 articles making up the scientific evidence base for use of Actovegin in muscle injury.

Our review returned only 1 original research article in the past 10 years to evaluate the efficacy of Actovegin as an

TABLE 2. Outlining the Key Articles Investigating Preclinical Evidence and Mechanisms of Action

Study	Type of Study	Model	Method	Results	Conclusions
Astashkin et al, 2012	In vitro	Peripheral blood of patients (n) having heart failure Class II-III of NYHA (New York Heart Association). SK-N-SH human neuroblastoma cell culture at 125 000 cells/mL.	Lucigenin (final concentration 30 μM) was added to blood samples (100 μL) to induce spontaneous formation of oxygen radicals. Formation of superoxide anions was in response to the bacterial tripeptide fMLP. Actovegin was added at 1 mg/mL, 4 mg/mL, and 8 mg/mL increment doses.	Actovegin inhibited the background effect of fMLP (3 μM from 2051 ± 100 impulses/s to 1930 ± 141 impulses/s 1 mg/mL AV), and to 1480 ± 62 ($P < 0.05$) impulses/s (4 mg/mL AV) and to 125 ± 13 ($P < 0.05$) impulses/s (8 mg/mL AV).	It is proposed that the protective effect of Actovegin is not only due to a decrease in the superoxide anion level, but also by neutralizing highly reactive hydroxyl radicals.
Yurinskaya et al, 2014	Review	SK-N-SH cells were grown in 24-well plates (200 000 cells per well in a volume of 1 mL). ROS formation was induced through treatment of cells with hydrogen peroxide.	Actovegin was added at 1, 2, 3, 5, and 10 mg/mL. Formation of ROS was measured using nitroblue tetrazolium (NBT).	Actovegin added to cells before hydrogen peroxide, reduced ROS formation. Cell incubation with Actovegin reduced apoptosis from 43% to 17%. A significant protective effect was observed even at a concentration of 1 mg/mL; the maximum protective effect at 5 and 10 mg/mL. The protective effect of Actovegin was completely eliminated when the inhibitors of 2 protein kinases (p38MAP and PI3) were used.	It is proposed that Actovegin reduces ROS-induced cell apoptosis by means of p38MAPJ and PI-3K inhibition. Early intervention with Actovegin may be beneficial.
Lee et al, 2010	In vitro	Serum-free monocytes skeletal muscle cell cultures were used. THP-1 cell line and macrophage derivative cultures were used, in total 10 cultures of 1.6 $\times 10^5$ cells.	2 mL ampules of Actovegin 40 mg/mL. Cell count was used to assess effect of Actovegin incubation on cell lines. qPCR was used to identify inflammatory modulators within the increase in macrophage cell lines.	After 24 h of incubation, both Actovegin and control groups in the THP-1 cell culture showed significant increases in cell counts. The Actovegin group showed 39% additional increase in THP 1 cell count compared with control ($P = 0.0001$). Significant changes in RQ values were observed; mean $CD68^+$ was 73% in the Actovegin group. $CD163^+$, MCP-1, and TNF-α were significantly higher in the Actovegin group, 147%, 133%, and 137% respectively.	Actovegin modulates the inflammatory process by influencing the $CD68^+$ and $CD163^+$ macrophages and $CD163^+$ THP-1 cells, which could influence the muscle healing process.
Hundsberger and Pfluger (Unpublished Observations) cited by Machicao et al, 2012	In vitro	CellSensor human embryonic kidney cell line, NF-κB-bla HEK 293T.	Actovegin or placebo solution with a salt concentration equimolar to Actovegin. Observation of the stably transfected β-lactamase reporter gene under control of the NF-κB response element	Measurement of fluorescence emission revealed that Actovegin activates the reporter gene of NF-κB expression in a dose-dependent manner. The effective concentration corresponded to the stimulatory effectiveness of a TNF-α concentration of approximately 400 pg/mL	It is proposed that the antiapoptotic properties of Actovegin may be attributed to transient activation of NF-κB
Gulevsky et al, 2008	In vitro	RK-15-IEKVM and VNK-21 clone 13/04 cell lines.	Treatment groups included 10% cattle blood serum, 2% cattle blood serum, or 2% cattle blood serum + 0.14% Actovegin. Proliferative and mitotic regimes of cells were monitored by increases in cell number and the number of dividing cells relative to the total number.	Addition of Actovegin stimulated proliferative activity of cells by 21% ± 3% in the first and third passages of the RK-15 cell line. Addition of Actovegin stimulated cell proliferation by 36% ± 3% in the VNK-21 cell line. Actovegin stimulated mitotic activity by 36% on day 1 and 48% by day 2.	The addition of Actovegin in low doses to a nutrient medium containing growth factors increases the bioenergetics state of cells. Further Actovegin may also be acting as a growth factor.

TABLE 2. Outlining the Key Articles Investigating Preclinical Evidence and Mechanisms of Action *(Continued)*

Study	Type of Study	Model	Method	Results	Conclusions
Gulevsky et al, 2011	In vitro	Healthy donors' whole stabilized blood and nucleated cell suspensions (suspension of leukocytes).	Actovegin 40 mg at 0.15 mg/mL or 1.5 mg/mL or cattle cord blood below 5 kDa. Phagocytic activity was assessed through 1-day co-culture with *Staph. aureus* and a neutrophil to bacterial ratio calculated. Bactericidal activity was assessed using an induced NBT test.	Incubation of frozen-thawed leukocytes in rehabilitating media of CBF or Actovegin at 1.5 mg/mL did not reduce the quantity of phagocytizing neutrophils. After 120 min of incubation with Actovegin or CBF, the phagocytic number of neutrophils dropped drastically suggesting that Actovegin and CBF activate engulfing and digesting functions of neutrophils. The index fold increase was 1.26 with Actovegin.	Recovery of functional activity of frozen-thawed neutrophils was possible with Actovegin therapy.
Buchmyer et al, 2011	Review	Two Authors, employees of Nycomed.	No review methodology.	Insulin-like activity and glucose metabolism. Improve oxygen uptake, metabolism, and hypoxia. Enhance wound healing and effect radiation-induced damage. Improve disturbances of blood circulation. Neuroprotective effects.	Actovegin has proven its efficacy in a variety of preclinical experiments. IPOs most likely under Actovegin's mode of action.
Lee et al, 2011	Review	Welshbone, South Wales Orthopaedic Network	Literature review of MEDLINE, PubMed, Embase, Science Direct, Scopus, Cochrane Library, and Google up to "2010" for the term Actovegin.	Improvements in redox balance of cells by promoting oxidative metabolism. IPOs are a putative ingredient in Actovegin having an insulin-like effect on glucose transporter activity. Actovegin has synergistic effects on cell proliferation demonstrated by epidermal, fibroblast and endothelial cell growth factors. Actovegin demonstrated membrane stabilizing effects in ischemic cells. Actovegin can regulate the expression of cell surface receptors of macrophages.	Active ingredients of Actovegin need to be identified. However, it is a licensed drug across Europe to treat stroke and diabetic neuropathy. Future work should look into the role of Actovegin in the inflammatory process in muscle repair.

IPO, inositol phosphate oligosaccharide; qPCR, quantitative PCR; NF, nuclear factor; TNF, tumor necrosis factor; AV, actovegin; RQ, relative quantity; MCP, monocyte chemoattractant protein; CBF, cord blood fraction.

injection treatment for muscle tears.[25] The study performed by Lee et al aimed to investigate the effect of Actovegin on muscle injury in human participants through robust clinical trialling. Lee et al studied the effect of the standalone Actovegin therapy on return-to-play time in injured professional footballers. After accurate diagnosis of hamstring grade tear on magnetic resonance imaging, a total of 4 grade I and 3 grade II injuries were treated with Actovegin therapy. The control group consisted of 4 patients with grade I tears that elected not to undergo Actovegin therapy. A reported average reduction of 8 days ($P = 0.033$) in return-to-play was found in the Actovegin treatment group compared with controls for grade I hamstring muscle tears. Both Laupheimer et al and Reurink et al suggest that the study is limited being nonblinded and nonrandomized observational pilot studies, with subjective assessments for returning to play, something acknowledged by the authors.[26,28] However, in a field where randomized controlled trial (RCT) is not always possible, this study remains the most robust article to investigate the standalone treatment of Actovegin in players from the same elite football club with standardized intervention, physical fitness, and rehabilitation protocol.

This review returned 2 articles concerning the safe use of Actovegin as an injection therapy. Reurink et al[26] performed a review of the myotoxic effects of various injection therapies, concluding that there was insufficient evidence to assess whether Actovegin was myotoxic or not. They concluded that nonsteroidal anti-inflammatory drug and local anesthetic intramuscular injections were myotoxic and that the evidence surrounding PRP was conflicting. The only other article returned in our search was a case report by Maillo et al,[27] who reported on a single case of anaphylactic shock in an amateur cyclist after intravenous infusion with Actovegin. However, this case has been largely discredited, and the reaction attributed to bacterial contamination during infusion as the patient responded well after treatment with broad-spectrum

TABLE 3. Outlining the Key Articles Investigating Clinical Efficacy

Study	Type of Study	Participants	Method	Results	Limitations
Pfister and Koller, 1990	Clinical Trial	103 patients (68 treated with Actovegin; 35 placebo)	Three injections in the injured muscle every 3–4 days.	Full sports activity was reached in the Actovegin group after 5.5 weeks, in the Placebo group after 8.3 weeks.	Outdated. Diagnosis was purely clinical and not graded according to magnetic resonance imaging. Patients recruited from various sports, and rehabilitation protocol not standardized. Actovegin was mixed with local anesthetics possibly altering pharmacodynamics. Subjective outcome measures were used.
Lee et al, 2011	Clinical Trial	11 injured professional footballers	7 players opted for Actovegin treatment; 3 intramuscular injection therapies and the same hamstring-specific rehabilitation protocol.	Players in the Actovegin treatment group were able to return to play 8 days earlier (95% confidence interval −1.249 to −14.7510) compared with physiotherapy alone (*P* 0.033).	A nonblinded and nonrandomized observational pilot study with subjective assessments for returning to play. Small study with limited power.

antibiotics. Furthermore, and although not necessarily pertaining to safe use in muscular injury, a large-scale RCT by Guekht et al explored the effect of Actovegin on poststroke cognitive decline. The findings of the ARTEMIDA study published this year concluded that after the infusion of 248 patients, the safety results were consistent with the good profile and tolerability demonstrated previously by the drug.[28]

Actovegin has demonstrated a good safety profile for the past 60 years in treatment of muscle injuries, diabetic neuropathy, and neurovascular conditions, which has been consistently demonstrated through large-scale clinical trials. This review has found no new or alarming evidence to suggest otherwise.

CONCLUSIONS

Review of the most recent literature suggests that Actovegin may be a promising intervention for athletes who experience muscular injury. Although current literature is yet to define the active compounds of the biological drug, its mechanisms of action are being demonstrated through antioxidant, antiapoptotic, and macrophage modulating in vitro properties. However, future research should look to investigate active components with the hope of influencing regulatory bodies. There is no new evidence to question the long-standing, good safety profile of Actovegin. The evidence investigating the ergogenic effect of Actovegin suggested that in vitro findings may not necessarily translate to meaningful outcomes in a clinical trial. Actovegin has been shown to be effective in reducing return-to-play time through 2 separate case series. This review has demonstrated that obtaining a wide base of evidence-based medicine remains difficult in a field where there is immense pressure to deliver cutting-edge therapies. However, regarding Actovegin, there have been improvements in the scientific evidence base surrounding its use, but further expansion and research are warranted. In conclusion, this review would suggest that, based on the most up-to-date literature, Actovegin is a safe injectable therapy that has demonstrated some efficacy in treating muscular sports injury and is unlikely to be ergogenic.

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