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Editorial

Bremelanotide-Like Agents, sGC Activators, Rho-Kinase Inhibitors, and Maxi-K Channel Activators: New Promising Remedies in PDE5-I-Failure Patients

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HIGHLIGHTS

- The pHLIP technology suggests numerous methods for progressive urinary tract cancer management.
- The pHLIP- ICG is used for diagnosis and transurethral resection of bladder cancer.
- The pHLIP- ICG is utilized to inhibit the growth of bladder cancer cells.

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ABSTRACT

Nowadays, the treatment strategy for erectile dysfunction (ED) is the same for all patients, ignoring the underlying etiology that can lead to Phosphodiesterase type 5 (PDE5-I) failure in a large (and increasing) subpopulation of ED patients suffering from diabetes mellitus, post-radical prostatectomy (RP) ED, hypogonadism, and Peyronie's disease. The uni-behavior among all of these novel drugs, except for PDE5-Is, is the ability to produce an erection without any demand for endogenous Nitric oxide (NO). It can be a promising forthcoming alternative for patients who are unwilling to current medical therapy. Melanocortin receptors (MCR) agonists and dopaminergic agonists have both shown promise in some early clinical trials. Bremelanotide-like agents potentially hold the most promise as centrally acting agents for the treatment of ED. Other peripherally acting agents, including the soluble guanylate cyclase (sGC), rho-kinase inhibitors, and Maxi-K channel activators, have all proved some clinical fruitfulness. Up to now, these novel agents have not yet reached the market. Nevertheless, it is likely that in years to come, patients will be selectively treated with these novel agents as a monotherapy or in combination with others acting synergistically.

Keywords: PDE5-I-failure; Bremelanotide-like agents; sGC activators; Rho-kinase inhibitors; Maxi-K channel activators

Editorial: Phosphodiesterase type 5 (PDE5-Is) has served as first-line treatment in the majority of patients, regardless of the etiology of their ED, with pharmacologic injections following as second-line medical therapy (1). Unfortunately, these treatments are not always effective, leading some patients to other lines or sometimes surgery. Excluding PDE5-Is is the ability to generate an erection without the need for endogenous Nitric oxide (NO). An alternative for patients who are unresponsive Erection: a complex event with many factors: initiation and maintenance. The "second-generation" PDE5-Is have been designed and introduced to provide greater specificity, efficacy, and diminished common side effects. In general, the agents effectively result in successful sexual intercourse rates of approximately 70%. There have been several scientific advances for innovative ED therapies in the last decade. Also, a combination of these therapies with PDE5-Is may help treat difficult-to-treat ED populations, such as PDE5-I non-responders (2).

Alternative oral Therapy

In the last two decades, significant advances have been

made in identifying molecular pathways and the agents that interact with these processes, all to provide informed treatment of ED. According to recent clinical trials and pre-clinical studies using human tissues, a centrally acting melanocortin receptor agonist or new peripherally acting agents, including the Max-K channel activator, guanylate cyclase activator, and NO donor have shown promising results in improving erection (3). Recent clinical trials suggest that regeneration therapy using SCs could also be a potential candidate for the treatment of difficult-to-treat ED populations, such as diabetic or post-prostatectomy ED like α-Adrenoceptor Antagonists (Phentolamine, Yohimbine hydrochloride (Yocon)), Dopaminergic Agonists (Apomorphine), Melanocortin-Receptor Agonists (Melanotan), Serotonin-Receptor Effectors (Trazodone (Desyrel)), l-arginine (the amino acid precursor of nitric oxide), L-dopa (dopamine precursor), Limaprost (prostaglandin E1), and naltrexone (opioid antagonist) (4).

Bremelanotide-like agents

Bremelanotide (formerly PT-141) is a synthetic analog of α-MSH and is the active metabolite of Melanotan-II (MT-II). Other molecular pathways have been more enigmatic to target. MCR agonists and dopaminergic agonists have both shown promise in early clinical trials. Bremelanotide-like agents potentially hold the most promise as centrally acting agents for the treatment of ED (5).

Subcutaneous form of delivery

Improvements in erection response in men with mild to moderate erectile dysfunction and in men with erectile dysfunction unresponsive to sildenafil, as well as improvement in both arousal and subjective excitement in premenopausal women. Other peripherally acting agents, including the soluble guanylate cyclase (sGC) activators, rho-kinase inhibitors, and maxi-K channel activators, have all demonstrated some clinical efficacy (5, 6). More importantly, these drugs act independently of NO production. Soluble Guanylate Cyclase Stimulators and Activators NO donors did not allow a constant and long-lasting cyclic guanylyl monophosphate (cGMP) stimulation and had a narrow therapeutic window. The stimulator sGC, riociguat, is on the market and is the only drug approved for the treatment of two forms of pulmonary hypertension (PAH/CTEPH), and a variety of other sGC stimulators and sGC activators are in preclinical and clinical development for additional indications. Rho-associated coil-forming protein kinase (ROCK) is involved in the generation of actin-myosin contractility and the regulation of actin cytoskeleton dynamics. It causes a contractile response in vascular smooth muscle cells by increasing Ca2+ sensitization. Studies have demonstrated that inhibition of tonic contraction of corporal smooth muscle by intracavernosal injection or topical application of Rho-kinase inhibitors to the penis results in increased blood flow into erectile tissue and causes an erection.

Smooth-muscle-specific gene transfer with the human maxi-k channel improves erectile function and enhances sexual behavior intracavernous injection of a smooth-muscle-specific gene transfer vector (pSMAA-hSlo) encoding the pore-forming subunit of the human large-conductance, calcium-sensitive potassium channel (Maxi-K). The potential utility of naked DNA-based gene transfer as an attractive treatment option for ED. According to recent clinical trials and pre-clinical studies using human tissues, a centrally acting melanocortin receptor agonist or new peripherally acting agents, including the Max-K channel activator, guanylate cyclase activator, and NO donor have shown promising results in improving erection.

Stem cell Therapy

Also, the combination of these therapies with PDE5-Is may help treat difficult-to-treat ED populations, such as PDE5-I non-responders. Recent clinical trials suggest that regeneration therapy using stem cells (SCs) could also be a potential candidate for treating difficult-to-treat ED populations, such as diabetic or post-prostatectomy ED. Stem cell therapy is a regenerative treatment aimed at restoring normal erectile physiology and curing ED. It is promising in cell-based and animal studies and has now been studied in humans (7, 8). Although the clinical results are not robust, future research may shed more light on the efficacy of this treatment for ED. The low-intensity extracorporeal shock wave therapy (LI-ESWT) showed favorable results have been proven.

Conclusions

There is growing evidence suggesting the efficacy of these emerging therapies, although most of the therapies need to be validated by well-designed clinical trials. It is expected that the emerging treatments can meet the needs of patients unresponsive to or unsatisfied with current therapies for ED once their long-term safety and efficacy have been confirmed. Meanwhile, LI-SWT showed favorable results as a monotherapy or in combination with SC therapy in treating patients with vasculogenic ED.

Authors' contributions

All authors contributed equally.

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Conflict of interest

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Data availability
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Abbreviations

cGMP	Guanylyl monophosphate
ED	Erectile dysfunction
MCR	Melanocortin receptors
MT-II	Melanotan-II
NO	Nitric oxide
ROCK	Rho-associated coil-forming protein kinase
sGC	Guanylate cyclase

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