Verteporfin: A Novel Antiproliferative Agent for Urinary Tract Fibrosis?

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Urinary tract fibrosis following injury, ischemia, or chronic inflammation can produce clinically significant obstruction, organ dysfunction, and debilitating urinary symptoms. Fibrosis is characterized by the excessive deposition of extracellular matrix, collagen, and glycoproteins by fibroblasts in response to the release of pro-fibrotic mediators such as TGF-β by macrophages[1]. This scarring often leads to the replacement of normal parenchymal tissue with fibrotic tissue, resulting in organ dysfunction and failure following chronic progression of this process[2]. Efforts to minimize fibrosis and scarring have implications for improving post-surgical outcome, preventing urinary organ dysfunction, and improving patient quality of life.

The objective of this paper is to review the mechanism of action of Verteporfin, prior clinical use, and potential avenues for urological implementation. Specifically, we seek to examine the novel use of this agent in urinary tract fibrosis.

The process of wound healing is divided into linear but overlapping phases including hemostasis/coagulation, inflammation, proliferation, and maturation. During the proliferation phase, wound contraction leads to the activation of tension sensing pathways[3]. Yes-associated protein (YAP) along with its transcriptional coactivator, TAZ, are activated and undergo translocation into the nucleus. In the nucleus, YAP/TAZ promotes the transcription of *Engrailed-1 (En1)* which then stimulates the conversion of *En1*-lineage-negative fibroblasts into *En1*-lineage-positive fibroblasts. These activated fibroblasts then drive the fibrotic response leading to increased collagen deposition and increased wound tension, thereby driving a positive feedback loop of proliferative fibrosis. The importance of the YAP/TAZ signaling pathway has also been elucidated in oncogenesis as overexpression has been linked to the proliferation of tumor cells. YAP is a critical component of the Hippo tumor suppressor pathway where it promotes growth factor independent proliferation, epithelial mesenchymal transition, and suppression of tumor necrosis factor[4]. As well, YAP overexpression has been linked to poor prognosis in some cancers, including urothelial carcinoma, secondary to its ability to confer resistance to cisplatin therapy[5]. Therefore, this molecular target has numerous potential clinical implications.

Verteporfin is an inhibitor of the YAP/TAZ pathway, whereby it binds to YAP and interferes with its interaction with TAZ, leading to downregulation of YAP and the fibrotic response[4]. As of 2000, the only approved clinical use of verteporfin by the U.S. Food and Drug Administration is as a photosensitizer for photodynamic therapy in the treatment of age-related macular degeneration. As a photosensitizer, it facilitates mitochondrial damage in target tissues through the generation of reactive oxygen species and anti-vascular endothelial growth factor (VEGF) activity[6]. However, its anti-tumor activity has been demonstrated to occur without the requirement for light stimulation[7].

Recently, the role of YAP/TAZ activation in renal tubulointerstitial inflammation and fibrosis following treatment with verteporfin was evaluated. A key component of renal fibrosis is release of the cytokine, TGF-β1. TGF-β1 is a potent mediator of fibrosis and therefore provides a critical therapeutic target for preventing the progression of renal fibrosis following acute kidney injury and subsequent chronic kidney disease development. Jin et al. investigated the effect of verteporfin on unilateral ureteral obstruction (UUO)-induced

Key Words

Verteporfin, fibrosis, urinary tract, inflammation

Competing Interests

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renal fibrosis. They found that verteporfin treatment of kidneys with UUO showed decreased levels of tubular dilation, inflammatory cell infiltration, and tubulointerstitial fibrosis compared with controls. As well, verteporfin treated kidneys with UUO exhibited an attenuated response with respect to α-smooth muscle actin and fibroblast specific protein-1 expression, which are central to renal fibroblast activation. Finally, the amount of type I collagen expression was reduced significantly in kidneys treated with verteporfin[8].

The anti-fibrotic activity of verteporfin has also been studied in relation to combination usage with triamcinolone acetonide, a corticosteroid with anti-angiogenic and anti-fibrotic properties mediated by the inhibition of proinflammatory prostaglandins and leukotrienes. Ophthalmological studies demonstrated a synergistic effect of verteporfin and triamcinolone acetonide[9]. Triamcinolone acetonide has been utilized in the treatment of urethral stricture disease and vesicourethral anastomotic stenosis, following incisional urethrotomy. As well, it maintains clinical applications in the management of pathologic phimosis and refractory interstitial cystitis. It may be that verteporfin is as efficacious as corticosteroids (or more so) for these indications, while avoiding the potentially serious adverse side effects.

Outside the urinary tract but within the scope of the genitourinary system, verteporfin has been evaluated in patients with Peyronie's disease. Mohede et al. treated biopsies of Peyronie's disease plaques obtained from 5 patients at the time of surgery with verteporfin and then examined the tissue by immunofluorescent staining for myofibroblast activity. Verteporfin was shown to reduce the expression of type I and IV collagen, fibronectin (component of the extracellular matrix), and LOXL2 and PLOD2, enzymes involved in collagen cross-linking which occurs during scar contraction. The reduced expression of PLOD2 leads to a softer scar, which in turn is more readily degraded by matrix metalloproteinases[10].

At present, verteporfin is approved for clinical use only in the photodynamic therapy of age-related macular degeneration; however, the potential applications of this agent extend far beyond ocular disease, given its regulatory role in the YAP/TAZ signaling pathway. Preclinical studies have provided early data regarding its use in the urological domain, both as an anti-tumor agent and in the attenuation of renal interstitial and Peyronie's disease fibrosis. Fibrosis and scarring can occur anywhere along the urinary tract leading to pain, infection, and obstruction, necessitating chronic indwelling stent and catheter placement. Attempts to mitigate scarring and prevent organ dysfunction and failure are paramount in mitigating increasing morbidity and mortality in patients. There may be a role for verteporfin treatment of urinary tract fibrosis and scarring both in the primary prevention and secondary treatment setting. To answer these questions, additional studies are required to evaluate the effect of verteporfin on fibrotic strictures obtained from the urinary tract including the ureters, bladder, and urethra. If the attenuation and prevention of scar formation can be demonstrated on a preclinical basis, then perhaps verteporfin may prove a formidable antiproliferative option for the treatment and prevention of urinary tract fibrosis.

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