NEW EVIDENCE FOR EXOGENOUS GLYCOSAMINOGLYCANS TREATMENT OF 'CYSTITIS': IS THE FUTURE NOW?

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Disclosure: The authors have declared no conflicts of interests.
Received: 04.07.16 **Accepted:** 25.07.16
Support: The publication of this article was funded by IBSA. The views and opinions expressed are those of the authors and not necessarily IBSA.
Citation: EMJ. 2016;1[3]:70-75.

ABSTRACT

Chronic cystitis may be due to different known causes. Current basic science research has revealed a wide consensus that chronic cystitis may arise from a primary defective urothelium lining and in particular from a damage of its glycosaminoglycans (GAGs) component. The GAG layer is composed mainly of heparin, dermatan, the glycosaminoglycans, chondroitin sulphate (CS), and hyaluronic acid (HA) which adhere to the surface of the urothelium. The main components, CS and HA, play a central role in the urine barrier and antibacterial defence mechanisms. When the GAG layer loses its protective barrier function it translates into increasing permeability of the urothelium. The main consequence of this is that bladder inflammation may arise. Exogenous restoration of the GAG layer has recently become a new opportunity for the treatment of recurrent urinary tract infections, painful bladder syndrome or interstitial cystitis, and lower urinary tract symptoms after chemotherapy or pelvic radiotherapy. The aim of this paper is to update the literature about the use of exogenous for the treatment of cystitis.

Keywords: Urothelium, cystitis, intravesical instillation, sodium hyaluronate, chondroitin sulfate (CS), Ialuril®.

INTRODUCTION

Chronic cystitis may be due to different known causes such as recurrent urinary tract infections (UTIs), chemical or physical irritants, resulting from chemotherapy and radiotherapy for pelvic tumours, or to uncertain causes and aetiology as in the case of painful bladder syndrome and interstitial cystitis (PBS/IC). Although in the past the urinary bladder epithelium was classically thought of as a simple passive barrier, current basic science research has revealed a wide consensus that chronic cystitis may arise from a primary defective urothelium lining and in particular from damage of its glycosaminoglycans (GAGs) component.[1-3] In normal conditions, the GAG layer consists of a thick mucus layer of glycoproteins and proteoglycans on the surface of the urothelial cells. The GAG layer is also located in between the cells lines and even in the entire bladder wall. Within the mucus is a hydrophilic mucin layer in which water molecules are embedded, providing a good barrier against ions, solutes, water, and pathogens. The GAG layer is composed mainly of heparin, dermatan, the glycosaminoglycans, chondroitin sulphate (CS) and hyaluronic acid (HA) which adhere to the surface of the urothelium. The main components, CS and HA, play a central role in the barrier against urine and antibacterial defence mechanisms. These components do not simply float on the surface but instead are 90% attached to transmembrane proteins, core protein chains, and proteoglycans so that they are stabilised on the surface and allow water molecules to be embedded. During dysfunction of the GAG layer, the GAG layer loses its protective barrier function leading to increased permeability into the deep layers of the urothelium and bladder and consequently to inflammation

(cystitis). Exogenous restoration of the GAG layer has recently become a new opportunity for the treatment of recurrent UTIs, PBS/IC, and lower urinary tract symptoms after chemotherapy or pelvic radiotherapy. Recently, Lazzeri et al.[4] provided an update on the clinical use of GAG therapy starting in such different clinical conditions.

In 2016, two new and well-designed papers dealt with the role of GAGs in the treatment of cystitis. Ciani et al.[5] addressed the role of Ialuril® for the treatment of recurrent UTIs and Gacci et al.[6] reported the clinical use of exogenous GAGs in patients with post-radiation cystitis. The aim of this paper is to update the literature about the use of exogenous GAGs for the treatment of cystitis starting from the pathophysiology of GAGs dysfunction.

PATHOPHYSIOLOGY OF GLYCOSAMINOGLYCANS DAMAGE

Different causes may be considered in the early stage of GAG injury. Autoimmune diseases, chronic bacterial infections, chemicals such as anticancer drugs (cyclophosphamide or bacillus Calmette–Guérin [BCG] exposure), or radiation exposure can all result in urothelial GAG loss. Damaging this shielding layer would result in the loss of protective function and would allow both the normal (i.e. H+, K+, Na+, Cl-) and abnormal constituents of urine (i.e. metabolites of cytotoxic drugs or toxic substances excreted in urine) to come into direct contact with the subepithelial layers. This infiltration through the GAGs barrier defect can cause subepithelial layer inflammation and delay or prevent the healing of both the damaged bladder urothelial cells as well as the GAGs.[7] The GAGs healing failure, due to chronic pathological stimuli (i.e. recurrent UTIs or radiotherapy), leads to the activation of a specific subset of unmyelinated C fibres in the suburothelium.[8] They are peptide-containing fibres (substance P, neurokinin A and B, calcitonin gene-related peptide, and Bradykinin) and although they serve as primary afferents, they may play an important role in the regulation of the lower urinary tract by an efferent function.[8] The afferent function, mediated by the release of neuropeptides from their central endings, is involved in the regulation of the micturition reflex, pain sensation, and activation of the visceral reflex. The efferent function due to the release of substance P, calcitonin gene-related peptide, and tachykinins from peripheral endings regulate the smooth muscle contraction, immune cell migration, mast cells degranulation, and neurogenic inflammation. There is robust evidence supporting their role in bladder chronic inflammation.[4]

Furthermore, when the GAGs defect persists or its healing process fails, chronic stimulation of suburothelial tissues may result in visceral hypersensitivity of bladder C fibre nociceptors.[9] Clinically, the neuronal hypersensitivity, i.e. the exaggerated perception to normal stimuli, leads to allodynia: the perception of nociceptive stimulation which occurs for stimuli that would usually evoke an innocuous sensation (i.e. pain during bladder filling). It also leads to hyperalgesia: exaggerated pain sensation to a stimulation which is normally mildly noxious (i.e. high pain intensity for mild inflammation).

Based on such evidence the use of exogenous GAGs for early repair of the GAG layer has been suggested and investigated. The hypothetical mechanisms of action are complex and include inhibition of adherence of immune complexes to polymorphonuclear cells, inhibition of leukocyte migration, and aggregation, regulation of fibroblast and endothelial cell proliferation, and enhancement of connective tissue healing.[10]

UP-TO-DATE: THE CLINICAL EVIDENCE

Urinary Tract Infections

Almost 50% of women will experience at least one UTI in their lifetime and in 20–50% of these, the episode is followed by a second infection within 6 months.[11] In the USA, up to 15% of women develop UTIs each year, and one in four of those will have one or more recurrences. This condition however is not restricted to women, and it is estimated that the annual incidence of UTIs in males aged 17–79 years in the USA is 2.2%.[12] The symptoms of UTI, particularly when recurrent, impact on quality of life and productivity, affecting physical and emotional functioning, vitality, sexual and social functioning, and general health perceptions.[13]

Eradication of the infection has been the aim of current management strategies. Continuous or patient-initiated antimicrobial therapy is the current standard management practice for the treatment of acute UTIs and the prophylaxis of recurrent UTIs.[14] Agents include trimethoprim with or without sulphamethoxide, nitrofurantoin, cefaclor, cephalexin, norfloxacin, ciprofloxacin, and fosfomycin. Disadvantages of this choice of

treatment include the adverse effects associated with the antimicrobial agents and the increasing drug resistance.[15]

Despite our broad array of very successful antimicrobial agents, UTIs remain a complex clinical condition. Urothelial GAGs also play an important role in fending off infection, by virtue of forming a physical barrier as well as binding and encapsulating bacteria.

Currently, there are a range of commercially available intravesical formulations of exogenous GAGs. There are formulations containing a low concentration of HA (0.08%), a low concentration of CS (0.2%), or a high concentration of CS (2%). Exogenous GAGs, especially in the combination of HA and CS (Ialuril®, IBSA), were originally investigated for efficacy in patients with PBS/IC who had not benefited from other therapies.[16] Recently, Ialuril® showed efficacy and safety for the prevention of recurrent UTIs.[17]

Earlier observational studies showed that exogenous intravesical HA markedly reduced recurrences of UTIs[18,19] and were followed by a prospective study of the combination of HA and CS in patients with recurrent UTIs.[17] This randomised, double-blind, placebo-controlled trial of Ialuril® (four instillations at weekly intervals, then five instillations at monthly intervals) monitored the 28 patients randomised to Ialuril® and the 29 patients randomised to placebo for 12 months. Patients treated with active drug had fewer UTI recurrences, a longer time to recurrence, and a greater improvement in quality of life than patients in the placebo group. They experienced fewer episodes of UTI and a longer mean time-to-recurrence than patients receiving placebo (87% versus 10% and 185 versus 53 days; p<0.05, for both); the total number of UTIs experienced at 6 and 12 months was also significantly less (p<0.05) in the Ialuril® group. Symptoms (according to the Pelvic Pain and Urgency/Frequency [PUF] score) improved significantly and quality of life was also improved at 12 months (p<0.001).

De Vita et al.[20] compared exogenous intravesical GAGs to antibiotic prophylaxis for recurrent UTIs in 28 women; the intravesical treatment significantly reduced the recurrence of UTIs and improved urinary symptoms, quality of life, and cystometric capacity at 12-month follow-up. Results in the GAGs (Ialuril®) and antibiotic groups were: number of recurrences (1 versus 2.3; p=0.02), mean 3-day voiding (17.8 versus 24.2; p=0.04), symptoms according to visual analogue scale (VAS) score (pain: 1.6 versus 7.8; p<0.001), PUF score (11.2 versus 19.6; p<0.001), King's Health Questionnaire score (18.4 versus 47.3; p<0.001), and maximum cystometric capacity (380 versus 229 mL; p<0.001). As in the Damiano et al.[17] study, tolerability of Ialuril® formulation was good with no serious adverse events reported. Recently Cicione et al.[21] assessed the effectiveness of intravesical instillation of HA and CS as a non-antibiotic treatment option for prophylaxis of recurrent UTIs in female patients at seven European institutions.[21] They used an intravesical instillation of 50 mL HA 1.6% and CS 2% solution in 157 women with recurrent UTIs. UTI episodes decreased from 4.13±1.14 to 0.44±0.50 (p=0.01) at 12 months, while recurrent UTI time prolonged from 94.8±25.1 days to 178.4±37.3 days (p=0.01) at 12 months. An improvement in symptoms and quality of life was achieved.

The critical analysis of these studies offers some considerations. The number of instillations seems to be an important marker of success for intravesical administration therapy. Furthermore, in contrast to what happens with antibiotic prophylaxis owing to side effects and development of resistance, the effectiveness of GAG reinstatement therapy improves over time, with an even better expected comparative effectiveness profile in the long-run as showed by Ciani et al.[5]

Painful Bladder Syndrome and Interstitial Cystitis

To improve the integrity and function of the bladder lining, exogenous intravesical GAG replacement therapies are one of the treatment options for patients with PBS/IC, generally refractory to conventional therapy.[14]

Morales et al.[22] found a complete or partial response rate of 71% for up to 1 year. Recently Engelhardt et al.[23] observed a 50% complete bladder symptom remission after intravesical HA. Those patients who responded did not use additional therapy during the 5-year follow-up; 41.7% with symptom recurrence improved with HA maintenance.[23] Hanno et al.[24] reached a different conclusion. They carried out a double-blind, placebo-controlled, multicentre clinical study of different HA preparations (40 or 200 mg/cm^3) and they did not find any significant efficacy of sodium hyaluronate compared with placebo.

Steinhoff et al.[25] investigated the exogenous CS therapy efficiency by an open-label 12-month study. The authors found a response rate for symptom improvement of 67% in 18 patients with 40 mL instillations of CS 0.2% weekly for 4 weeks and then monthly for 12 months. A recently published randomised controlled trial (RCT) failed to show superiority of CS 2.0% over control after 6 weeks of treatment.[26]

Porru et al.[27] investigated the efficiency of intravesical CS/HA combination in 20 PBS/IC patients. A VAS for pain and urgency, number of void per day, mean voiding volume, Interstitial Cystitis Symptom Index, and PUF score improved compared with baseline. Cervigni et al.[28] seemed to confirm such results. They reported the long-term results of intravesical CS/HA therapy in 12 patients and showed the sustained efficiency for 3 years in terms of mean number of voids per day and mean volume per void with the confirmation of quality of life assessments. The same author confirmed such results in 2014.[29] In this study, 74 patients were treated with Ialuril® and 36 with RIMSO-50®. At baseline, mean pain VAS scores of 65.53 (standard deviation [SD]: 21.00) and 64.58 (SD: 20.53) were reported in the Ialuril® and the RIMSO-50 group, respectively. At the end-of-treatment visit, the response to treatment in terms of pain decrease from baseline was statistically significant in both groups, with a VAS score reduction of -39.27 (SD: 24.52) for Ialuril® and of -31.00 (SD: 26.38) for RIMSO-50. For the 59 patients in the Ialuril® and 31 patients in the RIMSO-50 group completing the follow-up period, the mean VAS reduction was of -43.71 (SD: 28.56) and of -33.65 (SD: 31.31), respectively. The results from voiding diaries and the questionnaire scores were consistent with pain reduction. There was a higher proportion of patients with adverse events in the RIMSO-50 (30.56%; 95% confidence interval [CI]: 13.61–43.45) than in the Ialuril® (14.86%; 95% CI: 6.86–23.27) group. A case of strangury and a case of suprapubic pain, both treatment-related, led to withdrawal of two patients, one per group.

Despite the limitations of most of those studies, findings confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of patients with refractory PBS/IC.

Chemo and Radio-Induced Cystitis

Cystitis can be induced by both radiotherapy and chemotherapy, and can be either acute or chronic.[30] The condition often results in storage-type lower urinary tract symptoms and haematuria. It is generally thought that damage to the GAG layer coating the urothelium is the initial trigger for development of cystitis. In order to prevent and/or treat such conditions GAG replenishment therapy with CS, heparin, HA, and a new combination of CS and HA (Ialuril®) have been used.

Shao et al.[31] randomised 36 patients undergoing radiotherapy for gynaecological malignancies to receive either HA or hyperbaric oxygen therapy. They found no significant differences between the two groups in terms of haematuria, voiding frequency, or VAS pain at 6, 12, and 18 months after treatment, except for a decreased frequency of voiding at 12 months in the HA group. Sommariva et al.[32] studied the effects of intravesical HA+CS in patients with symptomatic late radiation tissue cystitis. In this 12-month, prospective, longitudinal, non-randomised, investigative pilot study, patients with severe haematuria received daily instillations 5 days/week in Month 1, 3 days/week in Month 2, 2 days/week in Month 3, once weekly in Months 4–6, every 2 weeks in Months 7–8, every 3 weeks in Months 9–10, and monthly/bimonthly for 1 year. Patients with or without occasional haematuria received instillations 3 days/week in Month 1, 2 days/week in Month 2, 1 day/week in Months 3–4, every 2 weeks in Months 5–6, every 3 weeks in Months 7–8, and monthly/bimonthly for 1 year. A total of 32 patients were enrolled. Authors found interesting results. Starting from a mean baseline of 66.9 mL, bladder capacity significantly increased to 101.9 mL at 3 months and to 174.4 mL at 12 months ($p<0.001$ for both versus baseline). Voiding frequency also significantly decreased from 14.6/day at baseline to 10.5 at Month 3 and 8.8 at Month 12 ($p<0.001$ for both versus baseline). Significant increases were observed after 3 and 12 months for the quality of life as measured by the European Quality of Life 5-Dimensions (EuroQol-5D) and the EuroQol-5D VAS.

Giannessi et al.[33] investigated a group of patients with cystitis and nocturia related to post-radiation bladder pain. This study evaluated the impact of HA+CS on symptoms and bother related to nocturia in men with bladder pain syndrome. Authors concluded that HA+CS was effective in reducing nocturia and related bother after radiotherapy. Gacci et al.[34] confirmed such results. Although bladder instillation treatment with a combination of HA and CS can be considered effective in reducing nocturnal voiding frequency

in men with post-radiation bladder pain following prostate cancer, RCTs with sham treatment are needed to extend and validate results.

BCG-induced chemical cystitis unresponsive to conventional therapies represents a considerable challenge for clinicians. While BCG is considered to be an effective treatment to reduce recurrence and progression of non-muscle-invasive bladder cancer, it is indeed associated with local treatment-related side effects that can lead to discontinuation or interruption.

Imperatore et al.[35] investigated the effect of treatment for BCG-induced chemical cystitis unresponsive to traditional treatments with intravesical administration of HA+CS. At all follow-up times, significant improvements were seen in VAS scores for pain and urgency, voids per 24 hours, and urine volume per void. Significant improvements were observed throughout the 12-week study period. These authors concluded that intravesical instillation of HA+CS is an efficacious strategy for refractory BCG-induced chemical cystitis with results that appear to be long-lasting.

Finally, Topazio et al.[36] investigated if sequential administration of HA could reduce the side effects related to BCG. A total of 30 consecutive subjects undergoing BCG intravesical administration for high-risk non-muscle-invasive bladder cancer were randomised to receive either BCG alone or BCG+HA. Mean VAS score for pain was significantly lower in the group receiving the combination of BCG+HA. International Prostate Symptom Score and number of daily micturitions were all significantly lower in the group receiving BCG+HA.

All these approaches are very interesting and could offer a real alternative or a new protective treatment to post-radiotherapy tissue damage. However, most of the studies are not RCTs and do not include a control group. For this reason, caution is necessary in interpreting them. Furthermore, some open issues remain. The undefined schedule treatment, the prevalence of male population, different types of tumours, and small sample size requires new information before the introduction of this treatment to clinical practice. Currently an international study using Ialuril®, IBSA for the prevention of post-radiation pelvic syndrome is ongoing and results are expected in the next months.

CONCLUSION

Robust evidence indicates that a defective urothelial barrier may underlie or be involved in the pathogenesis of several chronic bladder conditions, such as PBS/IC, recurrent UTIs, and chemical and radiation cystitis. These different clinical entities that were in the past considered distinct diseases can now be viewed as diseases caused as a result of the dysfunction of a common physiological element, the urothelium and associated GAG lining.

This renewed approach to looking at the pathophysiology of these GAG disorders will allow the development of more effective treatments for these debilitating and sometimes chronic diseases. Preliminary studies of the intravesical instillation of a combined solution containing a high concentration of HA and CS as GAG replacement therapy suggest that this formulation has efficacy potential in both UTIs and PBS/IC. Importantly, the safety profile of this combination has been reported to be very favourable, without adverse events of particular significance. New emerging oral formulations could be a non-invasive and complementary approach, although no evidence exists till now.

REFERENCES

1. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology. 2007;69(4 Suppl):9-16.

2. Hauser PJ et al. Abnormalities in Expression of Structural, Barrier and Differentiation Related Proteins, and Chondroitin Sulfate in Feline and Human Interstitial Cystitis. J Urol. 2015;194(2): 571-7.

3. Engles CD et al. Intravesical chondroitin sulfate inhibits recruitment of inflammatory cells in an acute acid damage "leaky bladder" model of cystitis. Urology. 2012;79(2);483.

4. Lazzeri M et al. Managing chronic bladder diseases with the administration of exogenous glycosaminoglycans: an update on the evidence. Ther Adv Urol. 2016;8(2):91-9.

5. Ciani O et al. Intravesical administration of combined hyaluronic acid (HA) and chondroitin sulfate (CS) for the treatment of female recurrent urinary tract infections: a European multicentre nested case-control study. BMJ Open. 2016;6(3):e009669.

6. Gacci M et al. Bladder Instillation Therapy With Hyaluronic Acid and Chondroitin Sulfate Improves Symptoms of Postradiation Cystitis: Prospective Pilot Study. Clin Genitourin Cancer. 2016. [Epub ahead of print].

7. Hurst RE et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis.

Urology. 1996;48(5):817-21.

8. Maggi CA, Meli A. The sensory efferent function of capsaicin-sensitive neurons. Gen. Pharmac. 1988;19(1):1-43.

9. Dinis P et al. Anandamide-evoked activation of vanilloid receptor 1 contributes to the development of bladder hyperreflexia and nociceptive transmission to spinal dorsal horn neurons in cystitis. J Neurosci. 2004;24(50): 11253-63.

10. Iavazzo C et al. Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis? Eur Urol. 2007;51(6):1534-40.

11. Laupland KB et al. Community-onset urinary tract infections: a population-based assessment. Infection. 2007;35(3):150-3.

12. Guay DR. Contemporary management of uncomplicated urinary tract infections. Drugs. 2008;68(9):1169-205.

13. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002;113 Suppl 1A:5s-13s.

14. European Association of Urology. EAU Guideline 2015. Available at: www.uroweb.org. Last accessed: 25 July 2016.

15. Sorlozano A et al. Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: a 7-year surveillance study. Am J Infect Control. 2014;42(10):1033-8.

16. Cervigni M et al. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(7):943-7.

17. Damiano R et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol. 2011;59(4):645-51.

18. Constantinides C et al. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. BJU Int. 2004;93(9):1262-6.

19. Lipovac M et al. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynaecol Obstet. 2007;96(3):192-5.

20. De Vita D et al. Prospective observational study of intravesical sodium hyaluronate and chondroitin sulfate in women with chronic cystitis, recurrent bacterial cystitis: preliminary data. 86th SIGO Congress, Milan, Italy, 14-17 November 2010.

21. Cicione A et al. Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multicentre survey. Can Urol Assoc J. 2014;8(9-10):E721-7

22. Morales A et al. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol. 1996;156:45-8.

23. Engelhardt PF et al. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2011;22:401-5.

24. Hanno P et al., "Painful bladder syndrome (including interstitial cystitis)," Abrams PH et al., (eds.), Incontinence (2005) 3rd Edition, Paris: Health Publications Limited, pp.1456-520.

25. Steinhoff G et al. The efficacy of chondroitin sulphate 0.2% in treating interstitial cystitis. Can J Urol. 2002; 9(1):1454-8.

26. Nickel JC et al. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulphate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology. 2010;76(4):804-9.

27. Porru D et al. Impact of intravesical hyaluronic acid and chondroitin sulphate on bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2012;23(9): 1193-9.

28. Cervigni M et al. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: Long-term treatment results. Int Urogynecol J. 2012;23(9):1187-92.

29. Cervigni M et al. A randomized, open-label, multicentre study of efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate (HA 1.6% and CS 2%) vs dimethyl sulfoxide (DMSO 50%) in women with Bladder Pain Syndrome/ Interstitial Cystitis (BPS/IC). Abstract 464. EAU Annual Meeting, Stockholm, Sweden, 2014.

30. Payne H et al. Chemical- and radiation-induced haemorrhagic cystitis: Current treatments and challenges. BJU Int. 2013;112:885-97.

31. Shao Y et al. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012;109(5):691-4.

32. Sommariva ML et al. Intravesical hyaluronic acid and chondroitin sulphate improve symptoms and quality of life in patients with late radiation tissue cystitis: An investigative pilot study. Eur J Inflammation. 2014;12:177-85.

33. Giannessi C et al. Nocturia related to post radiation bladder pain can be improved by hyaluronic acid chondroitin sulfate (Ialuril®). Abstract 592. Eur Urol Suppl. 2014;13:e592.

34. Gacci M et al. Sodium hyaluronate and chondroitin sulfate replenishment therapy can improve nocturia in men with post-radiation cystitis: results of a prospective pilot study. BMC Urol. 2015;15:65.

35. Imperatore V et al. Intravesical instillation of sodium hyaluronate–chondroitin sulfate in patients with bacillus calmette-guérin-induced chemical cystitis unresponsive to conventional therapies: Preliminary experience with 1 year follow-up. Eur Urol Suppl. 2014;13:e466.

36. Topazio L et al. Could hyaluronic acid (ha) reduce bacillus calmette-guerin (bcg) local side effects? Results of a pilot study. BMC Urol. 2014;14:64.