GLYCOSAMINOGLYCAN-REPLENISHMENT THERAPY: RATIONALE FOR USE AND CURRENT EVIDENCE

Summary of Presentations from the IBSA Institut Biochimique SA Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 12th April 2014

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Introduction by the Chairman

Professor Phillip E. Van Kerrebroeck

The glycosaminoglycan (GAG) layer of the bladder represents a mucous layer on the surface of the urothelium. Acting as an antibacterial defence mechanism, the layer contains chondroitin sulphate, dermatan sulphate, and heparan sulphate.[1] Pathophysiological changes in this layer (including a lack of chondroitin sulphate), changes occurring after bacterial cystitis, chemo or radiation therapy, and overactive bladder (OAB) lead to the development of interstitial cystitis (IC).[2] The symposium presentations discussed the rationale for the use of GAG replenishment therapy in patients with bladder problems and outlined the challenges faced by clinicians when administering GAG therapy in the clinic.

The Physiological Function of the Urothelium – More than a Simple Barrier

Professor Paulo Dinis Oliveira

The bladder wall is composed of three main structures: the detrusor muscle, the suburothelium, and the urothelium. Sensory nervous innervation is abundant in the subendothelium, and fibres inclusively penetrate through the urothelium layer. This former layer also contains connective tissue, inflammatory cells, interstitial cells, and blood vessels, all of which sit on a layer of muscle cells. All of the elements of the sub-urothelial layer interact actively among them and with urothelial cells, forming a dynamic sensory organ participating in bladder function. The urothelial barrier is made up of a layer of mucopolysaccharides, the GAG layer, and the urothelium umbrella cells layer, both contributing to its function as one of the tightest epithelial barriers in the body.[3] Surface plaques are constituted by proteins known as uroplakins, and make up the so-called asymmetric unit membrane,

as the cellular membrane at the apical surface is thicker on the luminal side, and are important for transcellular permeability.[4] Surrounding the apical cells is a continuous network of tight junctions, predominantly made up of zona occludens-1 proteins, adhesins, and claudins. The GAG layer, also known as the mucous layer, is an important factor in cellular permeability. It is composed of a uniform mantle of GAGs and proteoglycans covering the luminal surface of the urothelium. Damage to this layer results in exposure of the underlying urothelial cells and can lead to bladder dysfunction.

GAGs are long chains of disaccharides, the most important of which are chondroitin sulphate, dermatan sulphate, and hyaluronic acid (HA). These GAGs rarely exist freely and are usually attached to a core transmembrane protein chain with a cytoplasmic tail. The attachment of several GAGs to this core protein chain makes up a structure known as a proteoglycan, which plays a principal role in various physical and chemical processes.

The GAG chain has the ability to retain water molecules, resulting in a 'gel-like' layer over the urothelium, which forms a seal giving protection against damage by cations and bacterial invasion. Proteoglycans are also involved in cell-cell adhesion, cell proliferation, cell differentiation, wound healing, and tissue remodelling. A recent study identifying urothelial GAGs has shown that chondroitin sulphate covers the layer of umbrella cells on the luminal side and is also present in the subendothelium, while heparan sulphate is only seen in the subendothelial space.[4]

Urothelial cells have neuron-like properties and produce neuromediators, which have autocrine and paracrine functions. These include acetylcholine, adenosine triphosphate, nitric oxide, nerve growth factor, substance P, and prostaglandins.[5–10] Under normal physiological conditions, signalling via these neuromediators regulates normal bladder function; however, under pathophysiological conditions, this signalling can lead to hyper or hyporeflexia, pain, and neurogenic inflammation.

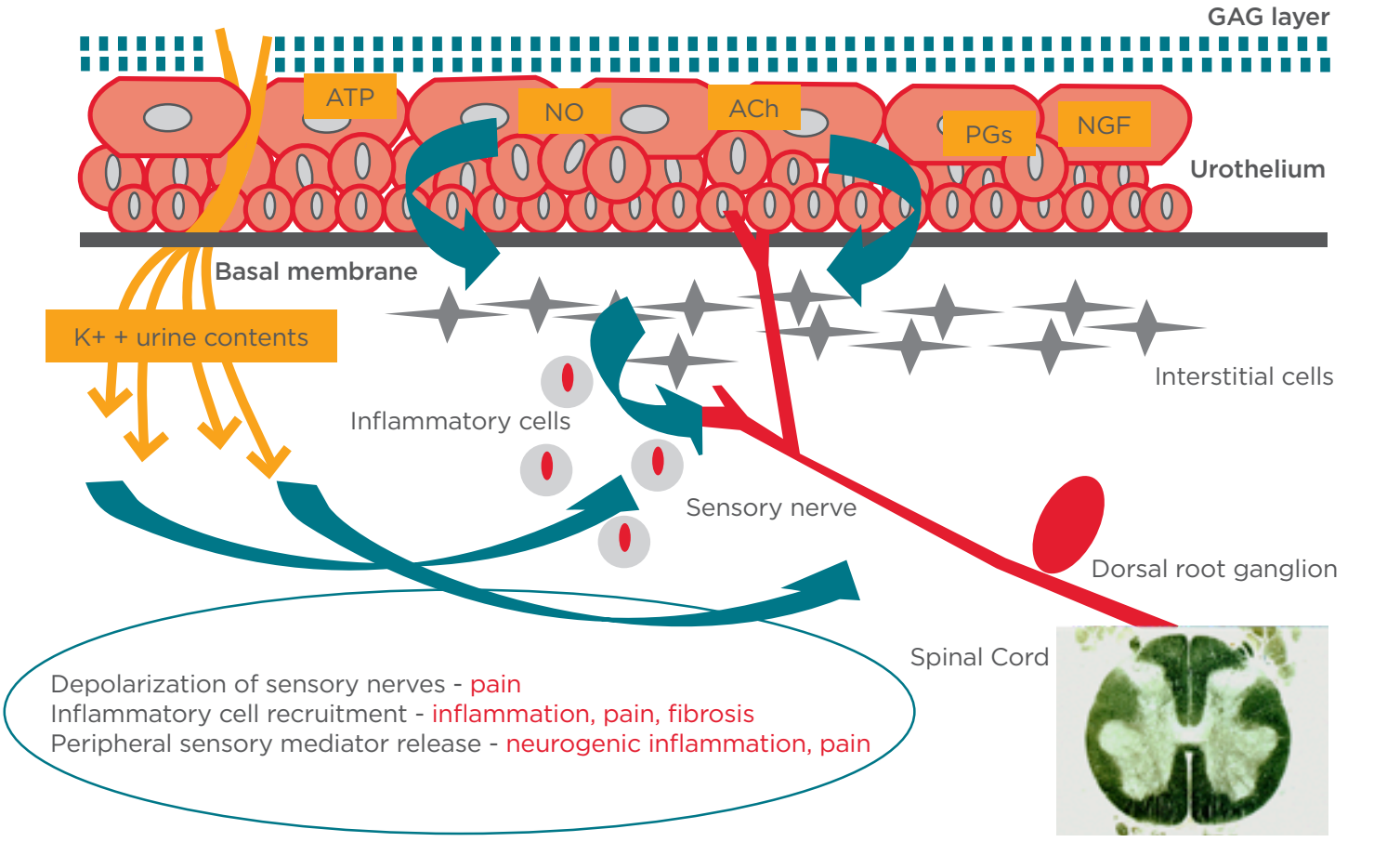

Figure 1: Glycosaminoglycan (GAG) layer/urothelium damage.
ATP: adenosine triphosphate; NO: nitric oxide; ACh: acetylcholine; PG: proteoglycans; NGF: nerve growth factor. From Paulo Dinis' presentation at this symposium.

A damaged GAG layer (Figure 1) is increasingly permeable to urine and its contents, in particular, potassium. An influx of potassium into the suburothelium leads to the depolarisation of afferent nerves that, in turn, leads to pain and neurogenic inflammation with subsequent recruitment of inflammatory cells. This cycle of events may at first be associated with acute pain and inflammation, but with time can lead to both chronic pain and inflammation, accompanying extensive damage to the GAG layer, with marked decreases in chondroitin and heparan sulphate.[11] Examination of urothelium and GAG layer in patients with bladder pain syndrome (BPS)/IC has shown a decrease in differentiation markers, such as chondroitin sulphate, E-cadherin, and tight junction proteins. This indicates a differentiation defect that can lead to a leaky urothelium due to increased permeability in these patients.[12] This increase in permeability is also apparent in the clinical setting.[13] A comparison of urinary potassium levels in patients newly diagnosed with BPS/IC and those previously treated for BPS/IC with GAG replenishment showed that the latter had higher levels of urinary potassium than newly diagnosed patients. This suggests that damage to this layer can be alleviated with GAG layer replenishment therapy, thus preventing potassium reabsorption.[13] Leakiness of the urothelium, as measured by the potassium sensitivity test, is also present in other diseases including: chronic pelvic pain, dyspareunia, vulvodynia, endometriosis, recurrent urinary tract infection (UTI), radiation cystitis, and some patients with bladder hyperactivity.[14]

Additional evidence suggests that application of an external GAG restores normal permeability by adhering to the damaged barrier whilst also inhibiting inflammatory cell recruitment.[2] The urothelium is therefore a complex structure with barrier and neuron-like properties that work in concert to regulate bladder function. GAG layer integrity is paramount to maintain normal urothelium and respective functions.

Economic Burden of Urothelium Dysfunction: The Case of Uncomplicated UTIs

Doctor Rosanna Tarricone

Recurrent UTIs (RUTIs) not only place a strain on patients but are also associated with increased demands on healthcare systems. This economic burden can be assessed from recent results of the ongoing RAISC-RUTI study.

Epidemiological data available on the occurrence of UTIs among females show that women with a previous history of UTIs have an increased risk of RUTI; 20–50% of initial episodes being followed by a second infection within 6 months.[16] UTI and RUTI episodes have a significant impact on quality of life (QoL) and adequate long-term treatments are not currently available. In recent years, development of newer therapies that work by replenishing the GAG layer offer a promising alternative to existing antimicrobial therapy. Although these alternative therapies are available, the economic costs and potential strain that they may place on already struggling healthcare systems must be carefully considered by policymakers.

An EU-based, multicentre, retrospective, case-control study sought to assess the costs and effectiveness of combined HA and CS (Ialuril®) versus the current standard management of RUTIs in adult women. In total, the study involved nine participating centres across four different countries. Baseline data included measurement of QoL using standard instruments including EQ-5D, the female sexual function index (FSFI), and the short-form 36 health survey (SF-36). Primary outcomes of this study included the occurrence of objective UTI recurrence, and secondary outcomes included the occurrence of symptomatic UTI recurrence and the mean direct overall costs associated with the two treatments over the two groups. Economic cost incurred by the two groups of patients will be calculated by assessing the use of resources associated with the two treatments. Preliminary data from this study are available from four of the nine study centres.

Preliminary results indicate a trend in favour of Ialuril; patients in this group had a 34% reduced risk of bacteriologically confirmed recurrence and a 23% reduced risk of having a symptom-based recurrence, compared to control (Table 1). Time-to-recurrence of bacteriologically confirmed recurrence was 357 days with Ialuril versus 302 days with standard of care.

Preliminary cost-effectiveness analysis has shown that laboratory examination and instrumental costs are slightly higher for Ialuril treatment versus the standard of care treatment. In contrast, the cost of hospitalisation and additional medical

Table 1: Retrospective case-control study of effectiveness of Ialuril versus the current standard management of reoccurring urinary tract infections in adult women.

Recurrence (binary) bacteriologically confirmed	OR (95%CI)	Adj OR (95%CI)*
Standard of care	*Reference*	*Reference*
Ialuril	0.66 (0.31-1.38)	0.63 (0.28-1.38)
**Adjusted for age, dyspareunia and EQ-5D*		
Recurrence (binary) clinical/symptoms based	**OR (95%CI)**	**Adj OR (95%CI)***
Standard of care	*Reference*	*Reference*
Ialuril	0.77 (0.37-1.60)	0.73 (0.34-1.61)
**Adjusted for age, dyspareunia and EQ-5D*		

From Rosanna Tarricone's presentation at this symposium.

therapies were lower for the group treated with Ialuril. It should be noted that these are preliminary data that represent a subset of patients in the study. Other factors to consider include the organisation of the different healthcare systems of the four participating countries in which these preliminary data were obtained, which may affect the overall cost incurred within each treatment group. However, the results emphasise the importance of assessing the cost-effectiveness of new treatments for policymakers.

Clinical Utility of GAG-Replenishment with IALURIL

Doctor Salvador Arlandis Guzman

Chemically-induced cystitis as a result of cyclophosphamide treatment, ketamine abuse, or Bacillus Calmette–Guérin (BCG) therapy for high-grade bladder tumours results in urothelium lesions and long-term damage to this layer. Similarly, radiation-induced cystitis can also lead to urothelium damage, as well as damage to the connective tissue and surrounding vasculature. The aetiology of IC/BPS is unknown but is thought to be multifactorial. Factors that may contribute to urothelium damage include allergy, infection, hypoxia, and autoimmune reaction. The disruption of the GAG layer, such as that seen during UTI, increases bacterial adherence and perpetuates the risk of further recurrence of UTIs. Therefore, replenishing the damaged GAG layer may offer a defence against further infection, and may play a role in chemical and radiation-induced cystitis and IC/BPS.

The rationale for using GAGs replacement therapy in RUTI comes from studies in rats treated for 5 days with HA, CS, or a combination of HA and CS, inoculated with *Escherichia coli* and sacrificed 3 days later for bladder examination. Animals that had received a combination of HA and CS showed increased bacterial resistance accompanied by a thicker transitional epithelium, providing promising results for the use of this therapy in humans. Other clinically relevant studies have shown promising data from the use of GAG replenishment therapy in patients with IC/BPS. Patients treated with Ialuril, which consists of a combination of HA and CS, for 8 weeks showed a significant improvement in pain, urgency, and frequency (PUF) score and a significant improvement in interstitial cystitis symptoms index (ICSI) score.[18] These results were also seen in a second study where combined intravesical therapy with HA and CS resulted in significant improvements in PUF score and the O'Leary–Sant score, which is used as a measure of symptoms associated with IC.[19] A 3-year follow-up study showed that GAG replenishment therapy has long-term benefits for PUF score and beneficial effects on all domains of the O'Leary–Sant questionnaire, including the bother index and the symptoms index.[20]

GAG replenishment therapy has also been shown to be beneficial in RUTI, with a 77% reduction in the occurrence of RUTIs versus placebo.[21] 48% of treated patients were relapse-free at the end of the study, whereas patients receiving placebo relapsed on average of 50 days; however, those receiving therapy were free from relapse for up to 6 months. Data from a systematic review showed reduced rates of UTI occurrence per year with

GAG replenishment, as well as a decrease in UTI recurrence and improvements in PUF score.[22]

There is a paucity of evidence available in the literature for GAG replenishment therapy in patients who have undergone radiation therapy. However, there is evidence showing that HA administration lowers bladder toxicity in patients who have undergone high-dose brachytherapy.[23] Similarly, CS instillation in patients who have received radiation therapy for gynaecological malignancies also reduces overactive bladder symptoms.[24] An investigation of 25 patients who had undergone radiation therapy, assigned patients to receive either HA or CS weekly for 6 weeks, and then once every 2 weeks for 2 months. Significant improvement was seen in International Prostate Symptom Score (IPSS), with improvements observed in International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), the bladder pain/interstitial cystitis symptom score (BPIC-SS), and QoL scores.[24] In addition, Ialuril therapy in patients undergoing treatment for BCG also showed a significant reduction in IPSS, indicating that Ialuril treatment in these patients could be used to counteract the chemical cystitis associated with this treatment.[25] Preliminary data on 25 patients show that Ialuril (once-weekly instillation for 12 weeks, with a mean follow-up of 6 months) significantly reduces visual analogue scale (VAS) pain scores and BPIC-SS. Improved responses were observed with primary treatments (in GAG therapy-naïve patients) versus rescue treatments (previous failure treatment with HA or DMSO); in the primary treatment group a 38% and 27% reduction was observed in VAS and BPIC-SS, respectively (Table 2).[26]

In order to choose the appropriate treatment in BPS/IC, characterisation of patient phenotype is of great importance. Identifying patients with urothelium dysfunction and GAG layer damage should improve outcomes after GAG replenishment therapy. Maintenance instillation policy may be

Table 2: Reduction in VAS pain scores and BPIC-SS with Ialuril in patients undergoing treatment for BCG.

Results				
Mean Age years (range)	**Time diagnosis** months (range)	**Primary/Rescue** (n/%)	**VAS pre** Mean ± sd	**BPIC-SS pre** Mean ± sd
60.4 (31-82)	20 (7.9-45.1)	15 (60%)/10 (40%)	6 ± 2.79	22.1 ± 8.2
			VAS post Mean ± sd	**BPIC-SS post** Mean ± sd
			5.3 ± 2.8	17,6 ± 10,3
			11.6% red. p=0.006	20.3% red. p=0.054
Primary versus rescue				
	VAS difference (pre-post)		**BPIC-SS difference (pre-post)**	
Primary	2.6 ± 2.1		7.1 ± 6	
Rescue	- 0.4 ± 1.9		- 0.3 ± 3.5	
p	0.005		0.023	
Primary versus treatment				
	Primary Treatment Group		**% Reduction**	**P**
VAS pre	6.9 ± 2.2		38%	<0.0001
VAS post	4.3 ± 3.2			
BPIC-SS pre	24.8 ± 5.8		27%	0.013
BPIC-SS post	18.1 ± 9.7			

Preliminary internal data non published, SURF HUP La Fe 2014

VAS: visual analogue scale; BPIC-SS: bladder pain/interstitial cystitis symptom score.
From Salvador Arlandis Guzman's presentation at this symposium.

useful, especially in patients who are refractory to previous treatments, but more studies are needed to confirm this hypothesis. Future lines of investigation should include new administration schedules (self-administration, daily), new indications (OAB, RUTI in neurogenic patients), and cost-effectiveness and cost-utility studies.

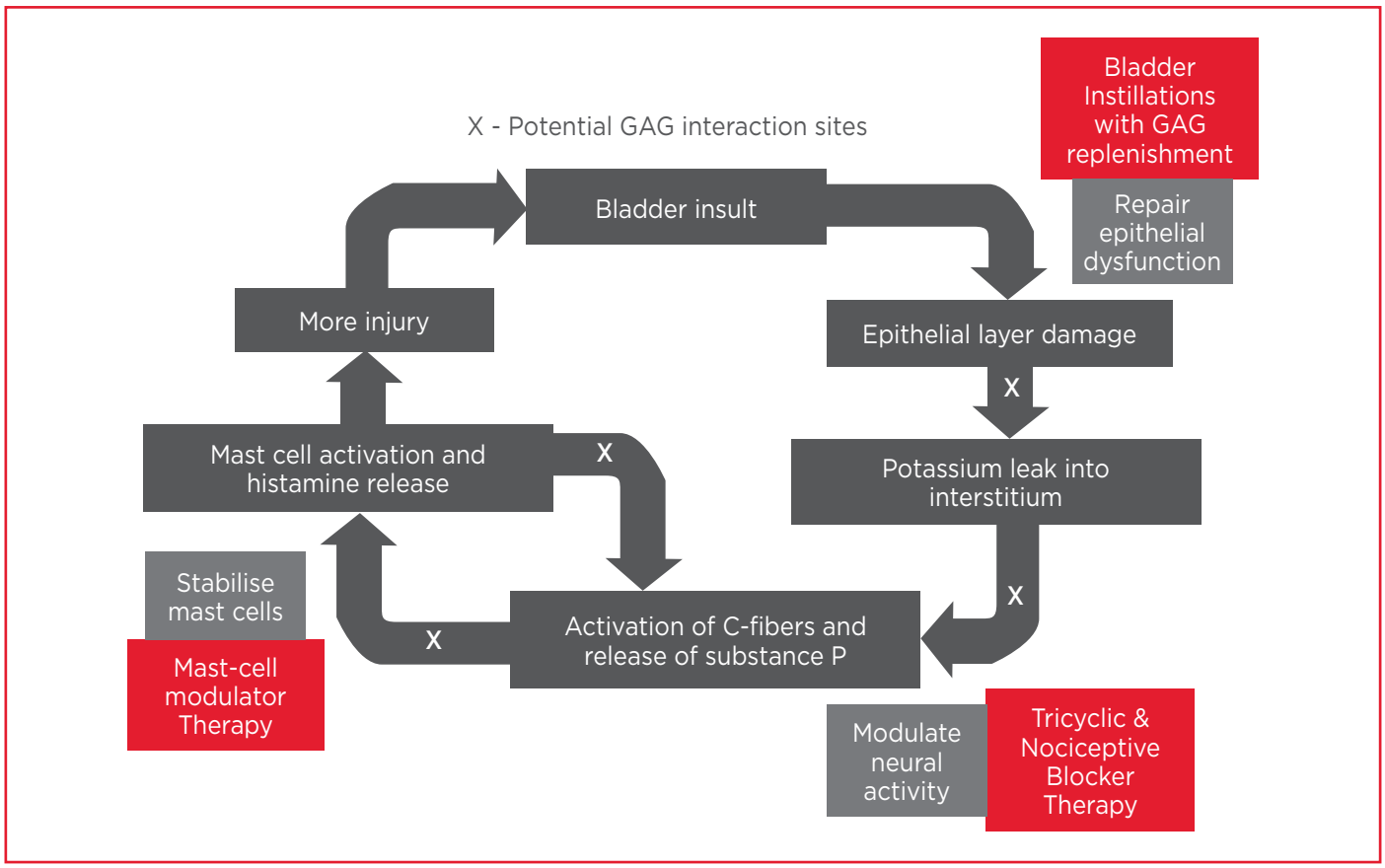

Figure 2: Principles of BPS/IC Therapy.
BPS: bladder pain syndrome; IC: interstitial cystitis; GAG: glycosaminoglycan.
From Mauro Cervigni's presentation at this symposium.
Modified from Evans RJ.[27]

Final Remarks

Professor Mauro Cervigni

The combination of HA and CS has overall beneficial effects on the GAG layer; HA reduces the pain in BPS patients while CS has similar effects in IC patients. The high concentration of HA and CS in Ialuril explains the therapeutic benefit of this treatment in patients who have a damaged GAG layer (Figure 2). It is important to identify the correct treatment regime, which is based on individual patient needs for optimal therapeutic benefit. In addition, the economic impact of the use of this therapy needs to be considered; whilst more expensive than the current standard of care, the therapeutic benefit that it could provide may outweigh the cost.

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