Neurourology and Urodynamics 32:9–18 (2013)

GAG Layer Replenishment Therapy for Chronic Forms of Cystitis With Intravesical Glycosaminoglycans—A Review

Helmut Madersbacher,[1]* Arndt van Ophoven,[2] and Philip E.V.A. van Kerrebroeck[3]
[1]*Department of Neurology, Medical University Innsbruck, Innsbruck, Austria*
[2]*Marienhospital Herne, University Hospital Bochum, Herne, Germany*
[3]*University Hospital Maastricht, Maastricht, The Netherlands*

Aims: Glycosaminoglycan (GAG) layer replenishment is a cornerstone in the therapy of interstitial cystitis (IC). During the last years intravesical GAG layer replenishment has proven to be an effective treatment for overactive bladder (OAB), radiation cystitis, and recurrent urinary tract infections (UTIs). **Methods:** Examination of different substances available for intravesical GAG replenishment and evaluation of the evidence for the treatment of the above-mentioned conditions. **Results:** We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) database for studies on intravesical GAG replenishment. A total of 27 clinical studies remain relevant to this topic, many of them with mixed patient selection and suboptimal definition of symptom improvement/success. Two placebo controlled studies with hyaluronic acid failed to show superiority and have not been published. One active controlled randomized study has been published showing that chondroitin sulphate 0.2% has a clear benefit for OAB patients. Another study with chondroitin sulphate 2.0% failed to show statistically significant evidence, but was underpowered. **Conclusions:** A short number of randomized controlled studies confirm efficacy of intravesical GAG layer replenishment therapy. Concluded from the study background (which comprises also uncontrolled studies), so far chondroitin sulphate 0.2% is in favor for intravesical GAG layer replenishment therapy. In general, large-scale trials are urgently needed to underline the benefit of this type of therapy. *Neurourol. Urodynam. 32:9–18, 2013.*

Key words: chondroitin sulphate; chronic cystitis; GAG layer; intravesical instillations

INTRODUCTION

Intravesical glycosaminoglycan (GAG) replenishment therapy is known for the treatment of interstitial cystitis (IC) since the late 1990s. Since then bladder pain syndrome (BPS)/IC as well as other forms of chronic cystitis have been treated with GAG replenishment, including radiation cystitis, recurrent bacterial cystitis, and lately as well overactive bladder (OAB).

The GAG layer was identified by Parsons et al.[1] as a mucus layer on the surface of the urothelium responsible for the antibacterial defence mechanism of the bladder. This mucus layer was further characterized by Hurst and Zebrowski[2] who could show that this GAG layer consisted mainly of chondroitin sulphate, dermatan sulphate, and heparin sulphate. Two years later it was shown by the same group that this GAG layer is defective in patients diagnosed with IC, particularly that there is a lack of chondroitin sulphate in the GAG layer of these patients.[3] Damage to the GAG layer has also been reported in patients treated with chemo- or radiation therapy and bacterial cystitis. A defect of the permeability barrier of the urothelium is documented for these conditions as well as for abacterial prostatitis and OAB.[4–6] GAG replenishment therapy has become a cornerstone in the treatment of IC[7] and has shown promising results in the treatment of several other forms of chronic cystitis associated with a GAG layer defect.

The following substances are used for intravesical GAG replenishment: chondroitin sulphate, heparin, hyaluronic acid, and pentosan polysulphate. Extensive clinical experience has been gained with formulations containing either chondroitin sulphate or hyaluronic acid. Recently, further formulations were launched, including a combination of chondroitin sulphate and hyaluronic acid. Thus, physicians might have difficulties in choosing the optimal treatment for their patients. Therefore, it makes sense to evaluate the different substances and the different products in particular. This review aims to clarify whether there are differences regarding efficacy and side effects, which do not only derive from the physical active substance but also from concentration and dosage form and—more important—to verify the evidence of their efficacy.

Abbreviations used: BPS, bladder pain syndrome; CFU, colony forming units; c_{max}, maximal bladder capacity; CS, chondroitin sulphate; CSI, CDI Severity Index; CDI, Chronic Disease Index; ESSIC, International Society for the Study of BPS; FDA, Food and Drug Administration; GAG, glycosaminoglycan; GRA, Global Response Assessment; HA, hyaluronic acid, IASP, International Association for the Study of Pain; IC, interstitial cystitis; ICI, International Consultation on Incontinence; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; IPSS, International Prostate Symptom Score; LUT, lower urinary tract; NaCl, sodium chloride; neg, negative; NIADDK, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; OAB, overactive bladder; OSPI, ÓLeary-Sant Symptom and Problem Index; PBS, painful bladder sydrome; pos, positive; PPS, pentosan polysulphate; PST, potassium sensitivity test; PUF, pain, urgency, frequency; QoL, quality of life; RCT, randomized controlled trial; UDI, urogenital distress inventory; UTI, urinary tract infection; VAS, Visual Analog Scale.

In this report, the term BPS/IC is used according to the ICI recommendations[33]; however, if an author used the term IC in his study we used it too.

According to Nordling and van Ophoven.[10] BPS/IC, OAB, radiation cystitis, and chronically recurring cystitis can be taken together under the term "chronic forms of cystitis."

Roger Dmochowski led the peer-review process as the Associate Editor responsible for the paper.
Conflict of interest: Yes.
*Correspondence to: Prof. Helmut Madersbacher, Department of Neurology, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria
E-mail: helmut.madersbacher@tilak.at
Received 27 September 2011; Accepted 13 March 2012
Published online 10 July 2012 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.22256

METHODS

A literature search was performed in the Medical Literature Analysis and Retrieval System Online (MEDLINE) database to retrieve studies on the intravesical use of GAG replenishment in the treatment of chronic forms of cystitis including July 2011. For retrieving the references in MEDLINE we used the following medical subject heading terms: IC, bladder pain syndrome (BPS), painful bladder syndrome, OAB, radiation cystitis, hemorrhagic cystitis, recurrent urinary tract infection (UTI), recurrent cystitis, or chronic cystitis in combination with chondroitin, hyaluronan, hyaluronic acid, heparin, or pentosan. Additionally two search criterions were chosen, either combination with the terms animal, in vitro, or preclinical in order to identify relevant preclinical data or combination with clinical study, randomized study, controlled study, clinical trial, observational study, non-interventional study, non-interventional investigation, case report, or intravesical treatment in order to identify relevant clinical data.

RESULTS

Intravesical Glycosaminoglycans in Animal Models

The MEDLINE search led to 38 hits, 35 of them not relevant to the subject of interest. A recently published study shows that instillation of chondroitin sulphate into a rat bladder restores the previously damaged permeability barrier, proving the concept of GAG replenishment in an artificial animal model.[8] Earlier the adherence of fluorescence-labeled chondroitin sulphate to damaged urothelium has been shown.[9] Although animal data for a clinical statement have to be used with caution, the qualitative statement—instillation of chondroitin sulphate restores the permeability barrier—seems to be justified. In contrast, transferring qualitative data from animal to humans, such as dosage finding studies is not justified.

Clinical data on Intravesical GAG Replenishment

The MEDLINE search led to a total of 123 hits. In the following only full text articles in English or with an English abstract were taken into account reporting on clinical data for intravesical GAG replenishment. Additionally, no studies were followed that evaluated the combination of treatments including intravesical GAG replenishment and other therapies such as hydrodistension. Thus, 27 relevant hits remained representing a number of 5 controlled studies and 22 uncontrolled studies.

Chondroitin sulphate. Chondroitin sulphate is available in several European countries with two different concentrations for intravesical application: 0.2% (40 ml) and 2.0% (20 ml). For chondroitin sulphate 0.2% a large non-interventional study has been published including 286 patients with mixed diagnoses (BPS/IC, OAB, radiation cystitis, and recurrent bacterial cystitis) showing significant improvement comparing baseline and endpoint values for urgency, frequency, and pain after 3 months of treatment. Eighty-two percent of patients and 84% of physicians gave a positive global rating on the treatment's effectiveness.[10] Additionally one uncontrolled study has been performed in patients with IC showing symptom improvement in 12 of 13 patients after 1 year of treatment.[11,12]

Furthermore, a randomized controlled single-centre study comprising 82 OAB patients (inclusion criteria: see Table I) shows superiority of chondroitin sulphate 0.2% over standard anticholinergic treatment with tolterodin tartrate (4 mg once daily) after 1 year of treatment. All patients had previously received one or more anticholinergics but not tolterodin. Unfortunately, this is not explicitly mentioned in the publication (personal communication by the first author of this publication). Seventy-two percent of patients in the GAG replenishment group reported improvement of symptoms in contrast to only 43% in the anticholinergic group.[13] This first part was published in 2006. The second and follow-up investigation another year later demonstrates a sustained effect for GAG replenishment: symptom improvement regarding frequency, nocturia, and urgency was still observed in 56% of patients for chondroitin sulphate in contrast to only 14% of patients in the anticholinergic group. Furthermore, quality of life was improved in the chondroitin sulphate group only.[14] These promising results certainly justify broader-based studies.

A recently published pilot study by Hazewinkel et al.,[15] showed that intravesical instillations with chondroitin sulphate 0.2% were well tolerated in patients undergoing radiotherapy. Moreover, these instillations showed improvement for the first time regarding the reduction of OAB symptoms (using VAS score for bladder pain and UDI for micturition) in this population of patients.[15]

An uncontrolled study with 53 IC patients demonstrates symptom improvement regarding response to treatment at week 10 compared to baseline for chondroitin sulphate 2.0% in 47% and 60% of patients at weeks 10 and 24, respectively.[16] In contrast, a recently published randomized controlled trial (RCT) failed to show superiority of chondroitin sulphate 2.0% over control after 6 weeks of treatment.[17] Although the difference in treatment effect was not statistically significant in this underpowered study many patients reported a clinical benefit. The authors further recommend to design a well-powered study.

Heparin. Heparin has been used off-label for GAG replenishment therapy. Two uncontrolled studies have been published. Parsons et al.,[18] documented symptom improvement in 27 of 48 IC patients after 3 months treatment with 10,000 U three times per week. A study published in 2001 evaluated urodynamic results in 40 IC patients treated with intravesical heparin 25,000 U twice a week for 3 months.[19] Twenty-nine patients showed symptom improvement of more than 50%, first sensation of bladder filling and maximal bladder capacity (c_{max}) improved (146 cc vs. 96 cc; 304 cc vs. 262 cc).

Hyaluronic acid. The product containing high-molecular weight hyaluronic acid (0.08%) is the ''oldtimer'' of products available. It is a non-sulphated GAG which is not present in the GAG layer of the bladder. A few uncontrolled or non-interventional studies including a total of 292 IC patients and two follow-up studies with overall 75 IC patients have been published showing symptom improvement in a rather broad range between 30% and 85% of patients.[20–28] Additionally, two studies demonstrate a reduction of acute UTI during GAG replenishment with hyaluronic acid, both showing a decrease of UTI events and an increase of time to recurrence (4.99 ± 0.92 vs. 0.56 ± 0.82 and 76.7 ± 24.6 days before after treatment vs. 178.3 ± 25.5 days after treatment, respectively).[29,30] Two case report articles show improvement of hemorrhagic cystitis in all eight patients without further details.[31,32] However, in double-blind, placebo-controlled, multicenter clinical studies of different hyaluronic acid preparations (40 or 200 mg/cc) no significant efficacy of sodium hyaluronate compared to placebo was found for IC patients.[33] Further details (e.g., patient selection, inclusion/exclusion criteria, definition of improvement/success) are not available from these studies.

Pentosan polysulphate. Pentosan polysulphate, a semi-synthetic GAG not present in the GAG layer of the bladder,

TABLE I. GAG Layer Replenishment Therapy—Overview of Relevant Studies

General study settings			General description				Findings		
Refs.	Study type	# of Patients, gender, Ø age ± SD or (range)	Indication	Major inclusion and exclusion criteria	Primary endpoint(s); tool(s)	Treatment intravesical	Key results	Level of evidence	Grade of recommendation
Controlled studies									
Bade et al.[34]	Double-blind, placebo-controlled	20, ♀, PPS (10): 53.8 y (24–75), placebo (10): 52.8 y (24–79)	IC	Incl. and excl.: IC with conformance to NIH criteria	Efficacy: frequency, nocturia, urodynamic capacity; VAS, bladder protocol	Group I: 300 mg PPS in 50 ml of 0.9% NaCl; Group II: placebo; twice a week for 3 months	Group I: statistically significant increase in c_{max}, improvement in nocturia, no change in frequency; Group II: no statistically significant differences before and after treatment	1b	B
Damiano et al.[38]	Prospective, randomized, double-blind, placebo-controlled	57, ♀, HA-CS (28): 35.1 y ± 11.9, placebo (29): 34.6 y ± 10.6	UTI	Incl.: at least 3 episodes of uncomplicated UTI within the last year, isolated $>10^3$ CFU/ml; excl.: >80 years of age	Rate of and time to UTI recurrence; PUF score, questionnaire on QoL	50 ml of 1.6% HA and 2.0% CS versus 50 ml saline; weekly for 4 weeks and then monthly for 5 months	HA-CS: significant decrease in UTI rate (77%); significant decrease in mean time to UTI recurrence (52.7 ± 33.4 days versus 185.2 ± 78.7 days)	1b	B
Gauruder-Burmester et al.[13]	Prospective, randomized, Tolterodine-controlled	82, ♀, Tolterodin (41): 49.3 y ± 12.3, CS (41): 51.7 y ± 9.8	OAB, definition see text	Incl.: premature urinary urgency, involuntary detrusor contractions, c_{max} <300 ml, voiding frequency >10/day, additional nocturia; excl.: stress and mixed urinary incontinence, other anatomical causes of OAB, neurological diseases, residual volume >100 ml	Efficacy: frequency, nocturia, urgency; questions on frequency, nocturia, urgency, satisfaction, side-effects, urodynamics, number of pads used, bladder protocol	Tolterodin tartrate 4 mg daily versus 0.2% CS instillations once a week for 1 month and then once a month until the 16th instillation; follow-up after 12 months	Improvement of symptoms (frequency, nocturia, pad numbers) in 43% (tolterodin group) and 72% (CS group)	1b	A
Gauruder-Burmester and Popken[14]	Retrospective, 2-year follow-up to Ref. 13	67, ♀, Tolterodin (35): 51.3 y ± 12.6, CS (32): 53.7 y ± 9.8	OAB, see above	n.a.	Efficacy: frequency, nocturia, urgency, quality of life; questionnaire on QoL, urodynamics	n.a.	Improvement of symptoms (see above) after 2 years in 14% (tolterodin) and 56% (CS); improvement of QoL in CS group only	1b	

(*Continued*)

TABLE I. (*Continued*)

General study settings			General description				Findings		
Refs.	Study type	# of Patients, gender, Ø age ± SD or (range)	Indication	Major inclusion and exclusion criteria	Primary endpoint(s); tool(s)	Treatment intravesical	Key results	Level of evidence	Grade of recommendation
Nickel et al.[17]	Prospective, randomized, double-blind, controlled	65, ♀, ♂, CS (33): 45.5 y ± 16.1, placebo (32): 44.4 y ± 14.9	IC/PBS	Incl.: conformance to NIH criteria of diagnosis, frequency of at least 11 per 24 hr; excl.: prescribed antihistamines, hormonal agonists, or antagonist therapies within the last 2 months	Efficacy and safety (no further details); GRA (to evaluate the overall change in patient's condition), questionnaires on QoL	20 ml of 2.0% CS versus saline; weekly for 6 weeks	6 weeks after therapy cessation: no statistically significant differences for the primary endpoint and for any of the secondary endpoints	1b	B
Uncontrolled studies									
Cervigni et al.[36]	Prospective	23, ♀, HA-CS: 46.5 y ± 13.6 (identical to [37])	IC/PBS	Incl.: IC diagnosis conforming to NIDDK criteria; excl.: no further details	Efficacy: frequency, urgency, pain, tolerability; VAS, questionnaires (ICSI, ICPI), voiding diary	40 ml of 1.6% HA and 2% CS; weekly for 20 weeks, then every 2 weeks for 4 weeks and then monthly for 3 months	Significant improvement in urinary symptoms on voiding dairies and VAS for frequency, urgency and pain; significant improvement in ICSI and ICPI	3	C
Porru et al.[37]	Prospective	23, ♀, HA-CS: 46.5 y ± 13.6 (identical to [36])	IC/PBS	Incl.: pain on bladder filling, pain (suprapubic, pelvic, urethral, vaginal, perineal), presence of glomerulation during hydrodistension; excl.: history of tumors, radiation cystitis, frequency <10/day, symptoms present <12 months	Efficacy: frequency, urgency, pain, tolerability; PUF, questionnaire (ICSI, ICPI), voiding diary	40 ml of 1.6% HA and 2% CS; weekly for 20 weeks and then biweekly for 6 months (single dose of oral antibiotics was administered before catheterization)	After 12 weeks: significant improvement in all ICSI, ICPI, and PUF scores, number of daily voids not significantly reduced	3	C
Cipe et al.[31]	Case study	1, ♂, 7½ y	Hemorrhagic cystitis in a hematopoietic stem cell recipient	n.a.	Efficacy and safety; description of symptoms	Two doses of 40 mg HA in 50 ml	Macrohematuria resolved within 4 days after the second dose	3	

(*Continued*)

TABLE I. (*Continued*)

General study settings			General description				Findings		
Refs.	Study type	# of Patients, gender, ∅ age ± SD or (range)	Indication	Major inclusion and exclusion criteria	Primary endpoint(s); tool(s)	Treatment intravesical	Key results	Level of evidence	Grade of recommendation
Constantinides et al.[30]	Prospective	40, ♀, 35 y (18–45)	UTI	Incl.: at least 3 episodes of uncomplicated UTI within the last year, isolated $>10^3$ CFU/ml; excl.: urethral stenosis, neurogenic dysfunction	Rate of and time to UTI recurrence; urine culture	40 mg HA in 50 ml; 5 months	Decrease of mean rate of UTI from 4.3 ± 1.55 to 0.3 ± 0.55; increase of time to recurrence: 498 days versus 96 days	3	C
Daha et al.[25]	Prospective	48, ♀, 54 y (22–82)	IC	Incl.: symptoms of urgency, frequency, pain, positive PST, conformance to NIH criteria with exception of c_{max}; excl.: UTI	Response to therapy, global bladder symptoms; urodynamics, VAS	40 mg HA in 50 ml; weekly for 10 weeks	Benefit in quality of life; Group I (c_{max} <350 cc): 27/32 (84%); group II (c_{max} >350 cc): 14/16 (87%)	3	C
Daha et al.[35]	Prospective, open label	29, ♀, 51.2 (22–60)	IC/PBS	Incl. and excl.: conformance to NIH-NIDDK criteria with exception of c_{max}	Response to treatment; VAS on QoL, OSPI	300 mg PPS in 50 ml; twice a week for 10 weeks	Reduction of VAS/OSPI; from 8.8/26.4 before to 4/15.3 after treatment; after 3 months: 3.8/15.2; after 6 months: 3.8/14; after 12 months: 3.4/12.1	3	C
Engelhardt et al.[28]	Retrospective, 5-year follow-up	48, ♀, 48.3 y (17–81)	IC/PBS	Incl.: conformance to ESSIC criteria, had been treated with 40 mg HA in 50 ml; excl.: "confusable diseases as the cause of the symptoms"	Efficacy (no further details); VAS on bladder symptoms	n.a.	50% (24/48): complete bladder symptom remission without any additional therapy; 42% (20/48): with recurrence, symptoms improved with HA maintenance therapy; 8% (4/48): no improvement	3	C
Gupta et al.[24]	Prospective	38, Gender not available; PST pos (23): 49.3 y ± 15.6; PST neg (15): 44.3 y ± 9.2	IC	Incl.: conformance to NIADDK criteria, PST performed; excl.: confirmed UTI, pelvic radiation	Response to treatment, determination of PST as predictor for IC; CSI, OSPI	40 mg HA in 50 ml; weekly for 6 weeks	Improvement of symptoms in 74% (17/23) PST pos patients and in 23% (3/13) PST neg patients	3	C

(*Continued*)

TABLE I. (*Continued*)

General study settings			General description				Findings		
Refs.	Study type	# of Patients, gender, Ø age ± SD or (range)	Indication	Major inclusion and exclusion criteria	Primary endpoint(s); tool(s)	Treatment intravesical	Key results	Level of evidence	Grade of recommendation
Hazewinkel et al.[15]	Prospective pilot-study, randomized	20,♀, intervention (10): 55 y (32–75), control (10): 64 y (47–93)	Radiation cystitis	Incl.: radiotherapy for primary or adjuvant radiotherapy for endometrial or cervical cancer; excl.: only brachytherapie, previous LUT surgery	Feasibility, efficacy (OAB symptoms); VAS, UDI on QoL	40 ml of 0.2% CS; weekly for 6 weeks during radiotherapy, control patients only questionnaire	Instillations were well tolerated by patients, decrease in OAB symptoms	2b	C
Kallestrup et al.[23]	Prospective pilot-study	20, ♀, n.a. (34–80)	IC/PBS	Incl. and excl.: conformance to NIDDK criteria	Response to treatment, efficacy: frequency, nocturia, pain; VAS	40 mg HA in 50 ml; weekly for 4 weeks and then once monthly for 2 months	Improvement of symptoms: no change in frequency, 40% (nocturia), 30% (pain), response rate: 65%	3	C
Kuo[19]	Prospective (urodynamic study)	40, ♀, 59.6 y	Frequency-urgency syndrome, IC	Incl.: frequency, urgency, pain; excl.: presence of UTI	Symptoms (first sensation of bladder filling), efficacy: nocturia, pain; adapted IPSS, urodynamics	25,000 U Heparin in 5 ml; twice a week for 3 months	Symptom improvement: more than 50% in 29 patients; less than 50% in 8 patients; first sensation of bladder filling (146 cc vs. 96 cc) and c_{max} (304 cc vs. 262 cc) improved	3	C
Lipovac et al.[29]	Prospective	20, ♀, 27.7 y (17–33)	UTI	Incl.: at least 3 episodes of uncomplicated UTI within the last year, isolated $>10^3$ CFU/ml; excl.: IC, neurogenic dysfunction, bladder carcinoma	Rate of and time to UTI recurrence; urine culture	40 mg HA in 50 ml; weekly for 4 weeks and then once monthly for 5 months	Decrease of UTIs: 4.99 ± 0.92 to 0.56 ± 0.82; increase of time to recurrence: 178.3 ± 25.5 days versus 76.7 ± 24.6 days	3	C
Miodosky et al.[32]	Prospective	7, ♀♂, n.a. (14–31)	HSCT, HC	Incl.: previous hematopoietic stem cell transplantation (HSCT), developed hemorrhagic cystitis (HC) grade ≥2	Efficacy, safety; description of symptoms	40 mg HA in 50 ml; one or two treatments	5/7: complete response; 1/7: partial response; 1/7: no response	3	
Morales et al.[21] Morales et al.[20]	Pilot study	25, ♀, ♂, 50 y (28–81)	IC	Incl. and excl.: conformance to NIDDK criteria	Response to treatment: urgency, pain; VAS	40 mg HA in 50 ml; weekly for 4 weeks and then monthly for 1 year (if initial response)	At week 12: 71% of patients report an improvement of symptoms	3	C

(*Continued*)

TABLE I. (*Continued*)

General study settings			General description				Findings		
Refs.	Study type	# of Patients, gender, Ø age ± SD or (range)	Indication	Major inclusion and exclusion criteria	Primary endpoint(s); tool(s)	Treatment intravesical	Key results	Level of evidence	Grade of recommendation
Nickel et al.[16]	Prospective	53, ♀, 44.1 y ± 15.2	IC	Incl.: conformance to ICDB (NIH) definitions, negative bacterial urine culture; excl.: pregnancy, lactation, other investigational drugs or treatments with defined time frames	Response to treatment: frequency, urgency, pain; GRA	20 ml of 2.0% CS; weekly for 6 weeks and then monthly for 4 months	Improvement of symptoms at week 10 in 47% of patients, at week 24 in 60% of patients	2b	C
Nordling and van Ophoven[10]	Prospective	286, ♀, ♂, 60.5 y (19–93)	Chronic forms of cystitis (BPS/IC, OAB, radiation cystitis, recurrent bacterial cystitis)	Incl.: clinical symptoms (frequency, urgency, pain); excl.: concurrent instillation therapies	Efficacy, safety, tolerability; numerical 11-point box scale, pain (IASP)	40 ml of 0.2% CS; weekly for 6 weeks and then monthly for 2 months	Significant improvement of urgency, frequency, and pain; positive global rating: 82% of patients and 84% of physicians	2b	C
Parsons et al.[18]	Prospective	48, ♀ ♂, 44 y (22–75)	IC	Incl. and excl.: conformance to NIDDK criteria	Response to treatment: pain, urgency, nocturia; numerical 6-point and 11-point box scales	10,000 U Heparin in 10 ml; 3 times per week for 3 months	After 3 months: 27 patients (56%) reported improvement of symptoms, in 21 patients (44%) no improvement	3	C
Porru et al.[22]	Prospective	10, ♀, 45.6 y (22–63)	IC	Incl.: clinical, urodynamic and endoscopic features of IC; excl.: no further details	Response to treatment: pain, frequency, nocturia; numerical 7-point box scale	40 mg HA in 40 ml; weekly for 6 weeks and then monthly for 6 months	Improvement of symptoms in 30% of patients at week 6 (maintained until week 24)	3	C
Riedl et al.[26]	Retrospective follow-up	121, ♀, 49.4 y (17–83)	IC/PBS	Incl.: confirmed IC, pos PST; excl.: no further details	Response to global bladder and IC symptoms, quality of life; questionnaire on QoL, VAS	40 mg HA in 50 ml; weekly	Symptom improvement in 85%, significant improvement of QoL in 81%	3	C
Steinhoff et al.[11] Steinhoff et al.[12]	Prospective	13, ♀ ♂, age not available	IC	Incl.: pos PST; excl.: neg PST	Response to treatment: pain urgency; questionnaires O'Leary, ICSP	40 ml of 0.2% CS; weekly for 4 weeks and then monthly for 12 months	6/13 (46,2%): good response; 2/13 (15,4%): fair response; 4/13 (30,8%): partial response; 1/13 (7,7%): no response	3	C

Classification according to evidence and grade guideline recommendations of the EAU based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001): www.cebm.net

is used as an oral treatment for IC, however, in Europe this is off-label use only. Two studies with intravesical pentosan polysulphate treatment have been published: one randomized placebo controlled study in 20 IC patients shows significant enlargement of c_{max} and improvement in night-time frequency after treatment for 3 months but no change in day-time frequency and in the volume of the first desire to void.[34] Preliminary data of an uncontrolled open-label study in 29 IC patients have been published in 2008, showing an improvement on the Visual Analog Scale (VAS) for quality of life from 8.8 to 4.0 after administration of 20 instillations during 10 weeks.[35]

Combinations of two glycosaminoglycans. The European market comprises two different formulations of a combination of two GAGs. The first one contains chondroitin sulphate (0.08%) and low molecular weight hyaluronic acid (0.08%). For this formulation no clinical data have been published so far. The second one contains chondroitin sulphate (2.0%) and low molecular weight hyaluronic acid (1.6%). There is one uncontrolled trial presumably published twice, however, since the completion of the study the product has changed.[36,37] Recently, there has been published one randomized, placebo-controlled study comprising patients with UTI showing a significantly reduced UTI rate and a significant decrease in mean time to UTI recurrence (52.7 $\pm$ 33.4 days vs. 185.2 $\pm$ 78.7 days) in treatment group. Limitations of this study are its monocentric design and the heterogeneity of patient characteristics.[38]

DISCUSSION

A major function of bladder epithelium is to provide an impermeable barrier to urinary solutes, such as ammonia, urea, potassium, and creatinine that are being excreted in the urine. The urothelium has several levels of defences against low and high molecular weight solutes, including the dense layer of GAGs and glycoproteins on the luminal layer, tight junctions, hydrophobic uroplakin plaques, and active ion pumps. It has been suggested that symptoms of IC and other forms of chronic cystitis arise from increased permeability of the bladder epithelium allowing these substances to penetrate and to trigger afferent nerve endings present in the basal layer of the urothelium and the suburothelium. Thus, they create the symptoms classically associated with BPS/IC, OAB, and other forms of chronic cystitis.[39]

The Mucin GAG-layer lining the bladder urothelium has an important role. It has been implicated in the pathogenesis of BPS/IC.[2] Recent findings suggest that the role of the GAG layer is to maintain a highly hydrated surface with barrier function. As such GAG layer replenishment therapy has been used successfully for nearly two decades in various forms. Despite wide empirical use and commercialization of the therapy the evidence of efficacy as well as the difference between GAG classes is not yet really established. GAGs fall into four main structural families: heparins and heparan sulphates, chondroitin and dermatan sulphates, and hyaluronate and keratan sulphates. In contrast to the others, keratan sulphate and hyaluronate are not components of the natural GAG layer; moreover, hyaluronate is distinct in that it is unsulphated and is usually not bound covalently to a core protein.

GAG layer replenishment therapy is widely accepted as a key therapy for BPS/IC and has shown to be effective also in the treatment of other diseases/syndromes associated with a possible GAG layer defect such as OAB. This is especially true for intravesical GAG layer replenishment therapy. The increasing interest in this therapy is reflected by the fact that four classes of substances, one of each with different concentrations, as well as two combinations of two substances and different dosage formulations are currently recommended and marketed by various companies. This matter of fact justifies the evaluation of efficacy and tolerability of the available formulations/substances.

The following substances are used for intravesical GAG layer replenishment therapy—chondroitin sulphate, heparin, hyaloronic acid, and pentosan polysulphate, and combinations of two GAGs (chondroitin sulphate and hyaloronic acid). Chondroitin sulphate, a natural component of the human GAG layer, with a good study background, is of special interest as it was shown that IC patients have a deficiency of chondroitin sulphate in the GAG layer.[3] A recent study on the distribution of exogenous chondroitin sulphate in several animal models of urothelial damage showed that the normal urothelium binds very little chondroitin sulphate, but the damaged bladder binds it avidly on the surface.[9] Hauser et al.,[8] proved the efficacy of restoring barrier function with chondroitin sulphate using the passage of an intravesically instilled radioactive marker Rubidium (^{86}Rb), a potassium ion mimetic, through the urothelium into the blood stream in a rat model of bladder damage. These findings support the use of GAGs for GAG layer replenishment therapy, especially for chondroitin sulphate. The mechanism of action therefore most probably arises from physical coating of the bladder surface and restoring impermeability as already claimed by Parsons.[4] The observed pattern of binding of chondroitin sulphate to damaged bladder suggests that its main action is a physical one on the urothelial surface and that GAG layer restoration is not due to a pharmacologic effect.

The efficacy of restoring the barrier function is proved in the animal model only for chondroitin sulphate but was not shown for other GAGs, although a similar effect may be possible.

Although large placebo responses have clouded clinical trials of replacement GAG layer therapy, thousands of patients have been treated with one of the formulations used for allegedly replacing the bladder GAG layer. The number of studies published is in general relatively small despite its first application in 1996. Existing data on the efficacy of intravesical instilled GAGs favor chondroitin sulphate 0.2% (40 cc): In addition to a small pilot study with IC a large, prospective, non-interventional study, comprising patients with clinically diagnosed chronic forms of cystitis proved that all main symptoms of chronic cystitis declined consistently and statistically significant. Moreover, it was well tolerated. Nevertheless, these results need to be confirmed in a controlled study. In a prospective randomized verum (tolterodine 4 mg) controlled study comprising OAB patients, intravesical chondroitin sulphate (0.2%, 40 cc) showed clear superiority over tolterodine 1 year after treatment for 12 months. However, these are the results of a single-center trial. If this treatment option for OAB patients is found to be effective in trials with larger cohorts, it would be a useful component in the treatment of OAB.

Based on the binding capacity studies in a mouse model of urothelial acid damage, the authors recommended a dosage of 400 mg chondroitin sulphate, diluted in 20 cc, therefore a 2.0% solution for intravesical treatment.[8] Two studies were conducted using this concentration and instillation volume. In a multicenter community-based real-life clinical practice study the authors suggested that intravesical chondroitin sulphate may have an important role in the treatment of IC and validated the rationale for a randomized placebo-controlled trial. However, in the prospective randomized double-blind

inactive vehicle-controlled 12-week study, there was no statistical significant difference of chondroitin sulphate 2.0% and the vehicle, probably due to the fact that this study was underpowered.[17] Additionally, a recently completed, placebo controlled study with chondroitin sulphate 2.0% for the treatment of IC did not meet predefined efficacy endpoint. These results let us assume, that there is no sign of superiority of a solution 2.0% over 0.2%. Both heparin and pentosan polysulphate have pharmacologic effects on the coagulation system. Heparin has been used off-label for GAG layer replenishment therapy, two studies comprise each a small number of patients and are uncontrolled.[18,19]

Hyaluronic acid (0.08%), although not a constituent of the human GAG layer, has been used since 1996 for intravesical treatment. Six uncontrolled or non-interventional studies, including two follow-up studies, showed inconsistent improvement rates between 30% and 85%.[20–28] Prevention of recurrent bacterial UTIs with intravesical instillation of hyaluronic acid was proved in two studies.[29,30] However, two placebo-controlled studies failed to show superiority over placebo and have not been published up to now.[33]

Pentosan polysulphate is a semi-synthetic GAG, which is also not present in the GAG layer of the bladder. It was used extensively for oral treatment in IC. It is the only oral drug, which is approved by the FDA for the indication IC. It was also applied intravesically with some success although the number of patients in the randomized placebo-controlled study is low and statistically significant improvement has been shown only for the bladder capacity (c_{max}).[34]

Based on the studies available, only for the intravesical application of chondroitin sulphate 0.2% and of pentosan polysulphate, randomized controlled studies showed significant improvement in patients with OAB and IC (both single-center studies). In regard to different concentrations of chondroitin sulphate there are no head-to-head studies comparing the efficacy of chondroitin sulphate 0.2% (40 cc) and 2.0% (20 cc).

Whether chondroitin sulphate alone or the combination of chondroitin sulphate and hyaluronic acid provides better expectations in regard to improvement/success is so far also not completely answered, since there is no study which compares the single substance to a combination of substances.

Based on available results, in particular chondroitin sulphate has the best study background and is so far in favor.[10–14] One large prospective non-interventional (comprising patients suffering from IC, OAB, radiation cystitis, and recurrent bacterial cystitis) and one randomized controlled study (comprising OAB patients) show statistically significant differences compared to an anticholinergic with an adequate number of patients included.

A combination of chondroitin sulphate and hyaluronic acid showed in UTI patients a reduction in UTI rate and a decrease in mean time to UTI recurrence.[38] Pentosan polysulphate has one randomized study with a small number of IC patients. Results of this study are a significantly increased c_{max} and an improvement in nocturia. However, there is no change in frequency.[34] Heparin has no controlled study.

CONCLUSIONS

Despite the fact that intravesical GAG replenishment is in use for about 20 years for BPS/IC and recently also for OAB and other forms of chronic cystitis, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, being or not being natural GAG layer components, dosage formulations, and concentrations. More important, there are differences in proved efficacy. Only for chondroitin sulphate, a combination containing chondroitin sulfate and hyaluronic acid and pentosan polysulphate RCTs are published. The largest numbers of patients documented in studies are published with chondroitin sulphate. But results are discordant: on the one hand, chondroitin sulfate 0.2% confirmed efficacy for OAB patients in a controlled study,[13,14] on the other hand the 2.0% solution failed to show efficacy in BPS/IC patients.[17] In controlled studies the level of evidence is 1b, the grade of recommendation is mostly B. Only one study and the related follow-up study using chondroitin sulphate can be recommended with A.[13,14] Uncontrolled studies are generally recommended with C (for details, see Table I).

It is well documented that intravesical instillations are a valuable and beneficial therapy, but distinct patient groups need to be confirmed by definite diagnostic findings. To get a clearer view on the efficacy of different GAGs, each of the formulations available should be evaluated in the future by randomized, controlled, and blinded clinical trials (possibly multicenter) with adequate patient numbers.

GENERAL REFLECTION UPON THE STUDY SITUATION

Literature search reveals a substantial lack of RCTs, the "gold standard" in clinical research. Therefore, it is understandable that uncontrolled and mostly poorly performed studies are likely to be discussed more prominent than they should deserve it. Preference is surely a crucial factor in many studies of the reviewed literature, however, certainly not a key problem of uncontrolled research. Moreover, it happens already before the publication is written, for instance at baseline or enrollment visits of patients suffering from a difficult disease, that evaluation of responses and drawn conclusions from that are going into one direction only. In addition, the range of different formulations of one drug and heterogeneous treatment regimen abets the affinity towards individually preferred therapy and displays the actual dilemma. If there was an obligatory rule how to treat a particular disease, one would know how to measure a new treatment or a new formulation. As there are no criteria for management, also the design of studies has deficits which make evaluation and conclusion for this review rather difficult. Furthermore, recommendations for intravesical GAG therapy do not suggest a definite formulation of a drug or a distinct treatment schedule.

Hence, as there are no criteria for the management, also the majority of available studies are poorly done. Large-scale RCTs are urgently needed to underline the benefit of this type of therapy.

REFERENCES

1. Parsons CL, Greenspan C, Mulholland SG. The primary antibacterial defense mechanism of the bladder. Invest Urol 1975;13:72–8.
2. Hurst RE, Zebrowski R. Identification of proteoglycans present at high density on bovine and human bladder luminal surface. J Urol 1994;152: 1641–5.
3. Hurst RE, Roy JB, Min KW, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 1996;48:817–21.
4. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology 2007;69:9–16.
5. Parsons CL, Albo M. Intravesical potassium sensitivity in patients with prostatitis. J Urol 2002;168:1054–7.
6. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 2001;57: 428–32.

7. Kurth KH, Parsons CL. The interstitial cystitis syndrome: Intravesical and oral treatment. Eur Urol Suppl 2003;2:2–9.
8. Hauser PJ, Buethe DA, Califano J, et al. Restoring barrier function to acid damaged bladder by intravesical chondroitin sulfate. J Urol 2009;182:2477–82.
9. Kyker KD, Coffman J, Hurst RE. Exogenous glycosaminoglycans coat damaged bladder surfaces in experimentally damaged mouse bladder. BMC Urol 2005;5:4.
10. Nordling J, van Ophoven A. Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis. A multi-national, multi-centre, prospective observational clinical trial. Arzneimittelforschung 2008;58:328–35.
11. Steinhoff G, Ittah B, Rowan S. The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 2002;9:1454–8.
12. Steinhoff G, Ittah B, Rowan S. The efficacy of intravesicular sterile sodium chondroitin sulfate 0.2% in potassium tested positive patients with interstitial cystitis. Adv Exp Med Biol 2003;539:731–9.
13. Gauruder-Burmester A, Wildt B, Tunn R. Treatment of overactive bladder with sodium chondroitin sulphate. Zentralbl Gynakol 2006;128:336–40.
14. Gauruder-Burmester A, Popken G. Follow-up at 24 months after treatment of overactive bladder with 0.2% sodium chondroitin sulfate. Aktuelle Urol 2009;40:355–9.
15. Hazewinkel MH, Stalpers LJ, Dijkgraaf MG, et al. Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies. Int Urogynecol J Pelvic Floor Dysfunct 2011;22:725–30.
16. Nickel JC, Egerdie B, Downey J, et al. A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis. BJU Int 2009; 103:56–60.
17. Nickel JC, Egerdie RB, Steinhoff G, et al. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology 2010;76:804–9.
18. Parsons CL, Housley T, Schmidt JD, et al. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994;73:504–7.
19. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. J Formos Med Assoc 2001;100:309–14.
20. Morales A, Emerson L, Nickel JC. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology 1997;49:111–3.
21. Morales A, Emerson L, Nickel JC, et al. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 1996;156:45–8.
22. Porru D, Campus G, Tudino D, et al. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. Urol Int 1997;59:26–9.
23. Kallestrup EB, Jorgensen SS, Nordling J, et al. Treatment of interstitial cystitis with Cystistat: A hyaluronic acid product. Scand J Urol Nephrol 2005; 39:143–7.
24. Gupta SK, Pidcock L, Parr NJ. The potassium sensitivity test: A predictor of treatment response in interstitial cystitis. BJU Int 2005;96:1063–6.
25. Daha LK, Riedl CR, Lazar D, et al. Do cystometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? Eur Urol 2005;47:393–7.
26. Riedl CR, Engelhardt PF, Daha KL, et al. Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:717–21.
27. Daha LK, Riedl CR, Lazar D, et al. Effect of intravesical glycosaminoglycan substitution therapy on bladder pain syndrome/interstitial cystitis, bladder capacity and potassium sensitivity. Scand J Urol Nephrol 2008;42: 369–72.
28. Engelhardt PF, Morakis N, Daha LK, et al. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2011;22:401–5.
29. Lipovac M, Kurz C, Reithmayr F, et al. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynaecol Obstet 2007;96:192–5.
30. Constantinides C, Manousakas T, Nikolopoulos P, et al. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: A pilot study. BJU Int 2004;93:1262–6.
31. Cipe FE, Soygür T, Dog˘u F, et al. Late onset hemorrhagic cystitis in a hematopoietic stem cell recipient: Treatment with intravesical hyaluronic acid. Pediatr Transplant 2010;14:79–82.
32. Miodosky M, Abdul-Hai A, Tsirigotis P, et al. Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate. Bone Marrow Transplant 2006;38:507–11.
33. Hanno P, Baranowski A, Fall M, et al. Painful bladder syndrome (including interstitial cystitis). In: Abrams PH, Wein AJ, Cardozo L, editors. Incontinence. 3rd edition. Paris: Health Publications Limited; 2005. 1456–520.
34. Bade JJ, Laseur M, Nieuwenburg A, et al. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol 1997;79:168–71.
35. Daha LK, Lazar D, Simak R, et al. The effects of intravesical pentosanpolysulfate treatment on the symptoms of patients with bladder pain syndrome/interstitial cystitis: Preliminary results. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:987–90.
36. Cervigni M, Natale F, Nasta L, 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: 943–7.
37. Porru D, Cervigni M, Nasta L, et al. Results of endovesical hyaluronic acid/chondroitin sulfate in the treatment of interstitial cystitis/painful bladder syndrome. Rev Recent Clin Trials 2008;3:126–9.
38. Damiano R, Quarto G, Bava I, 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: 645–51.
39. Parsons CL. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. BJU Int 2011;107: 370–5.