Madersbacher, H., van Ophoven, A. and van Kerrebroeck, P. E.V.A.:  

GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans—A review.

A search in the Medical Literature Analysis and Retrieval System Online (MEDLINE) database found 27 relevant studies related to the topic of GAG replenishment.

Basic research:

- The GAG layer consists mainly of the sulphated GAG's chondroitin sulphate, dermatan sulphate and heparin sulphate.
- Hyaluronic acid and pentosan polysulphate are not present in the natural GAG layer.
- The non sulphated GAG hyaluronic acid is usually not bound covalently to a core protein.
- Patients diagnosed with IC show a defective GAG layer with a deficit of chondroitin sulphate.
- 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; also the adherence of fluorescence-labeled chondroitin sulphate to damaged urothelium has been shown. The qualitative statement-instillation of chondroitin sulphate restores the permeability barrier-seems to be justified.

But transferring qualitative data from animal to humans, such as dosage finding studies is not justified.

- 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.

Clinical data

Chondroitin sulphate 0.2 %

- 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. 82 % of patients and 84 % of the physicians gave a positive global rating on the treatment effectiveness.

- An uncontrolled study in IC patients showed improvement in 12 of 13 patients after 1 year of treatment.

- One active controlled randomized study has been published showing that chondroitin sulphate 0.2 % has a clear benefit for OAB patients over tolterodin.

- A pilot study showed that intravesical instillations with chondroitin sulphate 0.2 % were well tolerated in patients undergoing radiotherapy, and showed improvement for the first time regarding reduction of OAB symptoms.
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**Clinical data**

**Chondroitin sulphate 0.2 %**
- An uncontrolled study with 53 IC patients demonstrates symptom improvement regarding response to treatment compared to baseline.
- An underpowered randomized placebo controlled study with chondroitin sulphate 0.2 % failed to show statistically significant evidence.

**Hyaluronic acid**
- 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.
- Placebo controlled multicenter studies in IC patients with different hyaluronic acid preparations failed to show superiority, further details on these studies are not available.

**Combinations**
- There is one uncontrolled trial of the combination 2.0 % chondroitin sulphate and 1.6 % hyaluronic acid, presumably published twice, however, since the completion of the study the product has changed. Recently, there has been published one randomized, placebo controlled study comprising patients with UTI showing a significant reduced UTI rate and a significant decrease in mean time to UTI recurrence in treatment group. Limitations of this study are its monocentric design and the heterogeneity of patient characteristics.

**Discussion and conclusions:**
- A short number of randomized controlled studies confirm efficacy of intravesical GAG layer replenishment therapy.
- The largest numbers of patients documented in studies are published with chondroitin sulphate.
- There is no sign of superiority of a chondroitin sulphate solution 2.0 % over 0.2 %. So far there are no head to head studies comparing the efficacy of both concentrations.
- 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.
- GAG replenishment therapy has become a cornerstone in the treatment of IC and has shown promising results in the treatment of several other forms of chronic cystitis associated with a GAG layer defect, UTI's, radiationcystis and OAB.
- The Gauruder-Burmester study in OAB patients versus tolterodin was the only A recommended study.
- To get clearer view on the efficacy of different GAG's, each of the formulations available, should be evaluated in the future by randomized, controlled, and blinded clinical trials (possible multicenter) with adequate patient numbers.
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