Application of hyaluronic acid in patients with interstitial cystitis

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Hyaluronic acid (HA, hyaluronan), a hydrophilic glycosaminoglycan (GAG) macromolecules with –COOH and –OH functional groups, as a member of the polysaccharides family, synthesized by HA synthases (three isozymes: HAS-1, HAS-2, and HAS-3) by repeated addition of glucuronic acid and *N*-acetyl-D-glucosamine groups (repeating the disaccharide unit of ß(1,4)-glucuronic acid (GlcUA)- ß (1,3)-*N*-acetylglucosamine) to the lengthening sugar and tightly catabolized by hyaluronidases, resulting in different molecular weight (MW) and variable half-life ($t_{1/2}$), plays a critical role in the extracellular matrix (ECM), because GAG is involved in many biological processes, such as pathogen/viral defense, coagulation, inflammation, wound healing, cell proliferation, cell adhesion, cell migration, morphogenesis, tissue integrity, tissue flexibility, and lubrication.[1–7] Except HA, all other members of the GAGs, including heparin/heparan sulfate, chondroitin/dermatan sulfate (a galactosaminoglycan group), and keratin sulfate, show different *N*- or *O*-sulfate patterns and are often conjugated with proteins, playing a part of the ECM in mammalian tissue and the constitutes of microorganism's polysaccharide capsule.[3,6,7] Nearly, all commercially used GAGs are still extracted from animal tissues.

HA is originally obtained from animal tissues, including bovine vitreous humors, rooster combs, the skin of sharks, and human umbilical cords.[3–5] However, animal origin HA may be contaminated by protein, nucleic acid, or microorganism, contributing to the adverse immunogenic response or the risk of transmitted disease. Therefore, chemoenzymatic synthesis has been advanced and developed, starting with the de novo synthesis and polymerization by Leloir glycosyltransferases using activated uridine-5′-diphosphate sugars, contributing to the production of HA by microbial HAS (mainly by *Pasterurella multocida*) or by enzymatic techniques.[4,5] HA is produced mainly by fermentation with *Streptococcus* strains, *Escherichia coli*, *Bacillus subtilis*, and others.[3–5] This chemoenzymatic synthesis strategy not only avoids the potential risk of immune response or disease transmission but also is mediated by producing a wide range of MW (ranged from 16 kDa to 2.5 MDa) to cover nearly all biological functions of HA. The biological function of HA is principally determined by their MW and size, mediated by binding to ECM molecules and cell surface receptors; thereby regulating cellular behaviors via control of the tissue's macro- and micro-environments.[3,5]

Due to the aforementioned characteristics of HA, including biocompatibility and high biodegradation, many HA-based medical and cosmetic drugs (bioengineering and biomedicine) have been grown up rapidly, and continue to grow the market to double-digit billion dollars amounts by 2027.[3] In fact, HA has been already and widely applicable in clinical practice, and is involved in the process of repairing, revitalizing and regenerating for many organs or systems. In gynecological systems as an example, bio-revitalizing skin (vaginal wall) cosmetics, endoprosthesis of pelvic organ prolapse or stress urinary incontinence, wound dressing, and anti-adhesive agents after surgeries have been well recognized in our daily practice.[8–13] We have attempted to use either auto-crosslinked hyaluronic acid (CHA, Hyalobarrier gel, Baxter, Pisa, Italy) or crosslinked hyaluronic acid platform (CHA-P) gel (PROTAHERE absorbable adhesion barrier, SciVision Biotech Inc., Kaohsiung, Taiwan) as adjuvant therapy after hysteroscopic myomectomy in patients with submucosal myoma and found that this intrauterine instillation of HA can effectively decrease the risk and/or severity of intrauterine adhesion in these patients after surgery.[11] A recent systematic review also favored the application of HA as an alternative to nonhormonal treatments for the signs or vaginal atrophy and dyspareunia, suggesting that HA has a profile of efficacy, safety, and tolerability comparable with vaginal estrogen in the management of postmenopausal women with atrophic vaginitis.[8] Therefore, the aforementioned findings raise our interest to comment the recently published article entitled "Factors associated with treatment outcomes after intravesical HA therapy in women with refectory interstitial cystitis: a prospective, multicenter study." which appears in the current issue of the *Journal of the Chinese Medical Association*.[14]

The authors attempted to evaluate the factor associated with nonresponse in women with refractory interstitial cystitis treated with intravesical HA instillation.[14] The authors found that functional bladder capacity before treatment was the statistical significance between the responders and nonresponders (172 ml vs 208 ml, $p = 0.049$).[14] Additionally, early response (1 month after treatment) was positively correlated with the late response (6 months after treatment) in patients with interstitial

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cystitis treated by intravesical HA instillation.[14] The current study is worthy of further discussion.

First, we should emphasize the importance of interpretation of results from any study, including Dr. Tsai's study.[14] The actual therapeutic efficacy should not be limited on the statistical significance (p value less than 0.05 as an example). The CI may be more powerful in the evaluation of its effect. Furthermore, the statistical significance should be carefully interpreted whether this "significance" is clinically meaningful. Many statistical significances may be totally absent of clinically meaningful value because the statistically significant finding cannot be transformed into clinical significance. Clinical significance should fulfill the following criteria to reach the extent of change, whether the change makes a real difference to subject lives, how long the effects last, consumer acceptability, cost-effectiveness, and ease of implementation.[15] We do not know how the authors calculated their sample size to finish this prospective, multicenter trial in the current study, but we believe that the even small effects appear statistically significant in the large sample size, because statistical significance is highly influenced by sample size.[15] The followings are an example. As shown by the authors, the mean functional bladder capacity of women enrolled in the current study was 223 mL (SD 93 mL).[14] The authors also found that the responders had the mean functional bladder capacity as 208 mL as well as the higher visual analog scale (VAS) of pain (mean 6.2, SD 2.8) compared to that the nonresponders had 172 mL mean functional bladder capacity as well as the VAS of mean as 5.6 (SD 3.0), but the authors concluded that both functional bladder capacity and VAS before treatment could predict the therapeutic outcome of intravesical instillation of HA.[14] There are at least two-weak points for the authors' interpretation about their data. One is that their data may be conflicted by each other. It is rationally believed that the severity of symptoms in patients with interstitial cystitis may have lower functional bladder capacity and higher VAS of pain. However, the responders were found to have a higher functional bladder capacity but a higher VAS. The discrepancy of both makes it the audience difficult to apply them to clinical practice. The other is that there is a doubt to show the difference between 208 mL and 172 mL as really clinically meaningful. With more interest, both data were apparently lower than that of the whole cohort (223 mL).[14] Furthermore, the SD was 103 mL and 102 mL, suggesting that the data are at high risk of overlap in both groups, although the authors said that the difference was statistically significant (p = 0.49).[14]

Second, the evaluation of the response was made at the end of the first month and the sixth month after treatment to show that 39.4% (54/137, defined as early responders) and 59.9% (82/137, defined as late responders) of patients had a response to intravesical instillation of HA. Among the early responders (n = 54), 14.8% of patients (n = 8) were finally ended by nonresponders at the 6-month follow-up. By contrast, among the early nonresponders (n = 83), 43.4% of patients would transform into the responders. Although the authors claimed that early response to intravesical instillation of HA can predict the final response (late response), we are wondering why the nonresponders at the first month of the end of treatment can be transformed into the responders without any further treatment during the additional 5-month period after intravesical instillation of HA. It is well known that early response to the treatment is an independent predictor for the successful treatment in many kinds of diseases, including cancers.[16] However, it is unusual to show that the absence of initial response can progress into the response after later.[17] For patients with interstitial cystitis, although it is a chronic illness, it is still hard to believe that no response of the initial therapy can be transformed into the response to treatment if no additional treatment is applied. Of course, some theories may explain the unusual finding. For example, a threshold hypothesis shows that the effect will appear when the accumulation dose (HA) reaches the therapeutic level. This accumulation of HA may trigger the regeneration process of injuries endothelium or epithelium of urinary bladder (interstitial cystitis), and restoration of normal function needs more time to reach. Additional 5 months make the restoration of normal function come true in patients with interstitial cystitis after intravesical HA instillation. The above-hypothesis can be used to support the authors' findings. In fact, the mean functional bladder capacity was dramatically increased when the follow-up period was longer, supported by 229 mL and 258 mL of the mean functional bladder capacity at the end of 1-month and 6-month follow-up, respectively.[14] In addition, the authors found that mean functional bladder capacity at the end of 6-month follow-up was statistically different from that baseline mean functional bladder capacity, supporting that the effect of intravesical HA instillation can slowly appear a few months later.

Although we may be confused by the current study's own to the conflicting data or their interpretation of results; there is no doubt that the significance of HA in health-promoting role is underestimated. The continuous advances in biotechnology mediated by the modification of HA which has been used in the revitalization process of the damaged or destructive tissue and organs may provide a vision in overcoming the ageing process-related health problems in the near future.

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