Abstract: An emerging theory regarding the potentially autoimmune nature of painful bladder syndrome/interstitial cystitis (PBS/IC) had led to several studies being conducted to assess the possible therapeutic effect of immunotherapeutic options for PBS/IC. This review presents the available evidence regarding the potential autoimmunity-based pathogenesis of PBS/IC and focuses on a main representative of the immunotherapeutic modalities for PBS/IC, aiming to summarize, evaluate, and present available data regarding the potential therapeutic role of monoclonal antibodies for PBS/IC patients. A non-systematic narrative and interpretative literature review was performed. The monoclonal antibodies included in the review were the anti-tumor necrosis factor-α (anti-TNF-α) agents adalimumab, which showed no difference compared to placebo, and certolizumab pegol, which showed statistically important differences in all outcome measures compared to placebo at the 18-week follow-up visit. Anti-nerve growth factor (anti-NGF) agents were also reviewed, including tanezumab, which showed both positive and negative efficacy results compared to placebo, and fulranumab, the study of which was discontinued owing to adverse events. In summary, monoclonal antibody therapy remains to be further researched in order for it to be proposed as a promising future treatment option for PBS/IC.

Keywords: PBS/IC, interstitial cystitis, monoclonal antibody, autoimmunity

Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) is an enigmatic clinical condition, predominant in females, with a reported heterogeneous and debilitating symptomatology.\(^1\) The most common clinical phenotype is characterized by suprapubic or pelvic pain, usually accompanied by urinary urgency, frequency, and/or nocturia, in the absence of infection or other pathological causes.\(^2\) Despite its previously reported negative medical and socio-economic impacts, PBS/IC remains the Achilles’ heel for many urologists as it is characterized by a lack of unanimously accepted nomenclature, pathophysiological pathways, and diagnostic and therapeutic algorithms.\(^3–5\)

Thus, it was absolutely expected that the controversies surrounding the definition, etiopathogenic mechanisms, and diagnostic protocol would finally lead to a variety of available PBS/IC treatment options.\(^6–8\) Unfortunately, the existing PBS/IC treatment armamentarium, covering a broad spectrum from lifestyle changes to oral medications, intravesical instillations, and surgical procedures, is not supported by robust scientific evidence regarding its safety or efficacy, highlighting the necessity for further high-quality research projects in this direction.\(^9\)

In this scope, an emerging theory regarding the potentially autoimmune nature of PBS/IC, expressed as either the emergence of non-specific or bladder-specific antibodies, and/or cell-mediated autoimmune disease, had led to several studies being conducted to assess the possible therapeutic effects of immunotherapeutic options for PBS/IC.\(^10\) This review focuses on a main representative of the immunotherapeutic modalities for PBS/IC, aiming to summarize,
evaluate, and present the available data regarding the potential therapeutic role of monoclonal antibodies in the currently unsolved puzzle of a valuable treatment option for PBS/IC patients.

**Methods**
A non-systematic narrative and interpretative literature review was performed. An extensive search using PubMed, Cochrane Library, and Scopus databases was conducted, retrieving English-language articles from inception to 30 December 2021, for studies exploring the effects of monoclonal antibodies on PBS/IC. The search terms included: “interstitial cystitis” OR (“painful bladder syndrome” OR “PBS/IC” OR “BPS/IC”) AND (“monoclonal antibodies” OR “immunotherapy” OR “adalimumab” OR “certolizumab” OR “tanezumab” OR “fulranumab”). The reference lists of all eligible studies, relevant reviews, and PBS/IC guidelines were also hand-searched. We included original RCTs and single-arm studies that investigated the clinical application of monoclonal antibodies for PBS/IC treatment in human adults. Original research articles investigating the use of monoclonal antibodies for other either related or unrelated medical conditions, such as chronic pelvic pain syndrome and prostatitis, were excluded.

**Autoimmunity: A Primary Suspect for PBS/IC?**
Several theories have been proposed, so far, to explain the underlying pathophysiological mechanisms of PBS/IC, with the autoimmunity-based hypothesis being one of the trending ones.\[11\],\[12\]

The trigger for the initial formulation of this theory was the epidemiological observation of existing similarities regarding the sex and age distribution of patients with PBS/IC compared to patients with other known autoimmune diseases.\[11\],\[13\] The autoimmunity-based pathophysiological mechanism of PBS/IC was further supported by the clinical concordance found between PBS/IC and various autoimmune syndromes, and also by the fact that PBS/IC is considered as a manifestation of some systemic disorders, such as irritable bowel syndrome, migraine, anxiety, and depression.\[14\]–\[16\] In addition, the autoimmunity-based theory around PBS/IC pathophysiology was fueled by the fact that autoimmune-originating characteristics, including episodic symptom flare and a relapsing and/or treatment-refractory nature, are frequently present in PBS/IC patients.\[10\]

Moreover, from a histopathological point of view, the common finding of urinary bladder infiltration by CD4+ T lymphocytes, mast cells, and eosinophilic leukocytes suggests an immune-mediated pathophysiological pathway for PBS/IC.\[17\] Mast cell activation and proliferation has been considered a crucial effector for the immune response in the pathogenesis of PBS/IC.\[18\] High numbers of mast cells are found in the suburothelial space of PBS/IC patients.\[19\] The activated mast cells secrete vasoactive neurotrophins and cytokines, which could lead to neuronal sensitization and secretion of neurotransmitters or neuropeptides, resulting in further mast cell stimulation. Because of this endless and vicious cycle, it is believed that PBS/IC is a pain syndrome with visceral and neuropathic characteristics.\[20\]

In addition, Peters et al.\[21\] proposed that an imbalance of type 1/type 2 helper T cells, as a result of immune system dysregulation, could represent a potential pathophysiological pathway of PBS/IC. A potential pathogenesis theory is also supported by the study of Ochs et al.,\[22\] in which the presence of a common autoantigen in the serum of both PBS/IC patients and patients with atopic dermatitis, a well-known type 2 T-helper cell-mediated skin disease, was highlighted. Moreover, the presence of higher urine concentrations (five-fold increase) of interleukin-6, a cytokine which enhances the type 2 T-helper cell response, in PBS/IC patients could also support a potential link between PBS/IC and autoimmunity.\[23\]

The hypothesis that there is a autoimmunity-based pathophysiological mechanism, expressed by a possible role of antimuscarinic M3 receptor (M3R) antibodies, leading to PBS/IC was reported by Van De Merwe and Arendsen.\[11\] The theory was supported by the fact that the presence of immunoglobulin G (IgG) autoantibodies to M3Rs is implicated in both Sjögren’s syndrome and PBS/IC and, moreover, by the presence of IgG autoantibodies against epithelium and muscle fibers reported in PBS/IC patients.\[24\],\[25\]

On the other hand, there are data proposing that the aforementioned immune reactivity is a response to bladder tissue damage and not the prominent cause of the inflammatory status observed in PBS/IC patients, and thus is not sufficient to classify the syndrome in the category of autoimmune diseases.\[26\],\[27\] In addition, the reported normal values of urinary bladder and blood lymphocytes, along with the absence of urinary interleukin-1β, are proposed as strong arguments against the autoimmune nature of PBS/IC.\[26\]
The bottom line is that no data exist, so far, to clearly support a solid etiopathogenic relationship between PBS/IC and a specific pathophysiological mechanism. Therefore, the immunological hypothesis cannot be rejected and, moreover, owing to the specific characteristics of the syndrome, holds an important role in the ongoing debate around PBS/IC pathogenesis. Nevertheless, further high-quality studies assessing the potential autoimmunity-based mechanism of PBS/IC are necessary to confirm or refute this theory.

**TNF-α Antagonism: Anti-TNF-α Agents**

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine released by immune cells. It is suggested to play a key role in the inflammatory process of PBS/IC. TNF-α is highly expressed in the bladder urothelium of patients with ulcerative PBS/IC and is found in significantly higher levels in the serum of PBS/IC patients than in controls. The increased expression of TNF-α and other proinflammatory cytokines in the serum of PBS/IC patients implies that besides mast cell activation, they may play an important role as inflammatory mediators in the pathogenesis of PBS/IC. Moreover, increased levels of TNF-α were reported in urine and bladder wash fluid samples of patients who were diagnosed with PBS/IC. According to previously published animal studies on autoimmune cystitis models, TNF-α inhibitors effectively decreased experimental PBS/IC bladder inflammation through the interruption of mast cell activation. In this scope, anti-TNF-α agents, such as adalimumab and certolizumab pegol, may decrease PBS/IC bladder inflammation and reduce symptoms by the inhibition of TNF-α and reduction of mast cell activation.

**Adalimumab**

Adalimumab belongs to a category of biological agents that are known as anti-TNF-α agents or TNF-α-blocking agents. Adalimumab is fully human, recombinant, monoclonal antibody acting through the neutralization of human TNF-α, and is indistinguishable from IgG. It is currently approved by the FDA for the treatment of several autoimmune diseases, including psoriatic arthritis, Crohn’s disease, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, and, more recently, ulcerative colitis.

Bosch et al evaluated the efficacy of adalimumab in the treatment of PBS/IC patients. A phase III, randomized, double-blind, placebo-controlled proof-of-concept study took place between March 2011 and March 2013. Men and women between the ages of 18 and 65 years, previously diagnosed with moderate or severe PBS/IC, were recruited. Patients in the active group (N=21) were given a loading dose of adalimumab 80 mg subcutaneously followed by 40 mg every 2 weeks for 12 weeks, while patients in the placebo group (N=22) received subcutaneous placebo for 12 weeks. Patients with moderate to severe PBS/IC treated with adalimumab demonstrated a significant clinical improvement in outcome measures compared to baseline. This improvement was clearly demonstrated in the O’Leary–Sant IC Symptom and Problem Indexes (p=0.0002), Pelvic Pain, Urgency, Frequency Symptom Scale (p=0.0017), and Global Response Assessment (GRA) (p<0.0001) at 12 weeks compared to baseline scores. Specifically, 53% (11/21) of patients in the adalimumab group had a 50% or greater improvement in the GRA at the 12-week follow-up visit. No serious adverse events were reported during the study period.

Nevertheless, adalimumab failed to demonstrate positive proof of concept for the treatment of PBS/IC compared to placebo owing to a significant placebo effect. This placebo effect has been repeatedly observed in PBS/IC trials. In particular, previous PBS/IC studies with a placebo RCT design had difficulty proving statistical significance. This reported higher placebo effect may represent the benefits of giving advice and support to the study participants. Future multi-center high-quality RCTs assessing the efficacy and safety of adalimumab are needed in order to further evaluate its potential role in the treatment algorithm of PBS/IC.

**Certolizumab Pegol**

Certolizumab pegol is a novel anti-TNF-α agent that has been used for treating autoimmune diseases. Theoretically, certolizumab pegol is considered to have advantages over other TNF-α antagonists as a potential treatment choice for PBS/IC. Certolizumab pegol is a recombinant, PEGylated, antibody Fab’ fragment with specificity for human TNF-α. As
a result of the conjugated polyethylene glycol its plasma half-life is increased, resulting in the inhibition of mast cell degranulation. It is characterized by a unique structure with different molecular properties. Thus, it is reported in the relevant literature that certolizumab pegol did not mediate apoptosis, it led to the inhibition of cytokine production, its distribution in inflamed tissue was higher, and the levels of neutralizing autoantibodies that developed were low. Certolizumab pegol resulted in a significant amelioration of the clinical signs and symptoms of autoimmune diseases, demonstrating at the same time a positive risk–benefit ratio.

In a double-blind RCT, the efficacy and safety of certolizumab pegol in the treatment of moderate PBS/IC symptoms were compared to placebo. The active group (N=28) received 400 mg of certolizumab pegol subcutaneously at weeks 0, 2, 4, and 8, while the placebo group (N=14) received the placebo treatment subcutaneously at the same timepoints. This study’s primary endpoint in GRA did not reach statistical significance at the 2-week follow-up visit. However, there were significant differences in GRA pain (p=0.002), GRA urgency (p=0.02), and GRA overall symptoms (p=0.006) by week 18. At week 18, certolizumab pegol demonstrated statistically important differences of −3.6 (p=0.03) for the Interstitial Cystitis Symptom Index, −3.0 (p=0.042) for the Interstitial Cystitis Problem Index, −2.0 (p=0.02) for the Pain scale, and −1.7 (p=0.03) for the Urgency scale, as well as a >30% reduction in pain (p=0.02). Taking these changes into account, certolizumab pegol appears to have clinical and statistical significance in the reduction of PBS/IC symptoms. This was also reported in a network meta-analysis assessing the efficacy and safety of pharmacotherapies for PBS/IC. According to this meta-analysis, certolizumab pegol was one of three treatment modalities, along with cyclosporine A and amitriptyline, that showed superior benefit compared to placebo. Moreover, apart from its effectiveness in PBS/IC, certolizumab pegol has been demonstrated to have an acceptable safety profile. Urinary infection was the most common reported adverse event, but all cases were resolved with the use of appropriate antibiotics based on urine cultures.

The previous study by the same author failed to prove the efficacy of adalimumab, probably owing to the significant placebo effect. In this scope, the present study included a treatment washout period of 1 month, which led to a decrease in the placebo effect on overall GRA from 50% in the previous study to an average of 14%. Moreover, the timepoint at which the primary endpoint was evaluated was a crucial factor. The period of 2 weeks were chosen based on the observed positive results of certolizumab pegol on rheumatoid arthritis by this time. However, the time period needed for a PBS/IC treatment modality to show significant improvement in women with moderate to severe symptomatology seems to be longer (up to 18 weeks), as PBS/IC represents a long-standing syndrome. Thus, further investigation is needed by conducting larger, longer, multicenter, randomized, placebo-controlled trials with phenotypic categorization of participants in order to accurately assess the efficacy of certolizumab pegol for the treatment of PBS/IC.

Anti-NGF Agents

Nerve growth factor (NGF) is one of the basic contributors to the survival of sensory and sympathetic neurons during development, and there is evidence that it acts as a peripheral mediator of various inflammatory painful conditions. It is produced by bladder smooth muscle and the urothelium in the urinary tract, and increased levels have been reported in the urine and bladder tissue of PBS/IC patients, indicating a predominance of specific pathophysiological pathways, especially sensitization of peripheral and central nerve endings. It regulates pain perception and, moreover, participates in the generation and maintenance of painful states, and specifically in bladder pain, based on animal model studies. In addition, NGF promotes bladder hyperactivity through the sensitization of peripheral and central nerve endings. Thus, in the search for alternative analgesics, NGF antagonism is gaining attention in research and development, with anti-NGF agents such as tanezumab and fulranumab being in the spotlight.

Tanezumab

Tanezumab is a humanized anti-NGF monoclonal antibody that binds with high affinity and specificity to NGF, preventing it from interacting with receptors on nociceptive neurons. Tanezumab acts by blocking the interaction of
NGF with its receptors, tropomyosin-related kinase A (high-affinity receptor) and p75 (low-affinity receptor).\textsuperscript{55} In a clinical trial setting, tanezumab improved pain scores, while also ameliorating function and patient global assessments in chronic painful conditions other than PBS/IC.\textsuperscript{56–58}

Evans et al\textsuperscript{59} evaluated the use of a single dose of tanezumab (200 µg/kg iv) or placebo for the treatment of moderate to severe PBS/IC pain. In total, 64 patients were enrolled in the study (tanezumab N=34, placebo N=30). The tanezumab group reported promising results regarding the improvement of pain symptoms, urgency episode frequency, and GRA compared to placebo at 6 weeks of administration. On the other hand, tanezumab showed no significant effect on the Interstitial Cystitis Symptom Index score, micturition frequency, or mean voided volume per micturition. The most common adverse events were headache (tanezumab 20.6%, placebo 16.7%) and paresthesia (tanezumab 17.6%, placebo 3.3%).

Nickel et al\textsuperscript{49} performed pooled analyses deriving data from three small clinical trials, including two already published studies\textsuperscript{59,60} and one previously unpublished study (ClinicalTrials.gov identifier: NCT00999518), including 208 patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and PBS/IC, to identify the best responders who are more likely to benefit from a tanezumab treatment scheme. Statistical analysis showed a statistically significant difference only in the reduction of pain in the group of women with PBS/IC, and patients with symptoms suggesting the concomitant presence of non-urological associated somatic syndromes compared to placebo, but no efficacy for the CP/CPPS patients. Taken together, these findings suggest that women with PBS/IC plus a non-urological syndrome could represent the target patient group that will most likely benefit from tanezumab treatment.

It seems that tanezumab may have limited capacity to induce an improvement in pain if NGF has limited to no involvement despite similar clinical presentations. This may explain why the benefits of tanezumab have been more apparent in women with PBS/IC. The use of combined data using a meta-analytical approach and performing subgroup analyses led to the conclusion that tanezumab represents a promising therapy for PBS/IC, although additional studies are required. This evidence could trigger more investigation into the role of NGF in the development of PBS/IC. The possible confirmation of this activity could promote tanezumab as an effective medication against pain in patients with PBS/IC.

Abnormal peripheral sensation was reported across the studies as an adverse event. The side-effect began within 2 weeks of initial tanezumab administration and resolved within 6–12 weeks. In clinical trials for other types of chronic pain using tanezumab, peripheral sensation has also been reported.\textsuperscript{56,57,61} This evidence does not match the expected pattern for a neurotoxic compound and does not suggest significant tanezumab neurotoxicity.\textsuperscript{62} However, the mechanism responsible for these adverse events of abnormal peripheral sensation has not been established.

Fulranumab

Fulranumab, a fully human recombinant monoclonal antibody (IgG), is a potent inhibitor of human NGF. Reviewing its efficacy in painful conditions other than PBS/IC, fulranumab showed a positive dose response in diabetic peripheral neuropathic pain, mixed efficacy results versus placebo, and statistically significant improvement versus an opioid in the pain of osteoarthritis, and did not show any benefit compared to placebo for low back pain.\textsuperscript{63–65}

A phase IIa study was conducted by Wang et al\textsuperscript{66} to explore the efficacy and safety profile of fulranumab, compared to placebo, in 31 patients with moderate to severe PBS/IC. However, this study was prematurely discontinued in 2010, owing to the fact that fulranumab studies were placed on clinical hold by the FDA because of a concern that the entire class of anti-NGF antibodies may be associated with a condition representing either rapidly progressing osteoarthritis or osteonecrosis. A single dose of 9 mg of fulranumab failed to promote analgesic activity, but these results are limited by the early termination and heterogeneity in the baseline study characteristics.

Table 1 summarizes the basic characteristics of the available human studies assessing the efficacy and safety of monoclonal antibodies for the treatment of PBS/IC.
### Table 1: Basic Characteristics of the Available Human Studies Assessing the Efficacy and Safety of Monoclonal Antibodies for the Treatment of PBS/IC

| Study      | Monoclonal Antibody | No of Patients (Mean Age) | Application Method | Assessment Tools | Efficacy                                                                 | Follow-up Duration | Limitations                                                                 |
|------------|---------------------|---------------------------|--------------------|------------------|---------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------|
| Bosch      | Adalimumab          | Active=21 (45.2 years) Placebo=22 (46.5 years) | Subcutaneous       | O’Leary–Sant ICSP1, GRA, Pelvic Pain, Urgency, Frequency Symptom Scale | No difference compared to placebo                                           | 12 weeks           | Heterogeneous population, Small sample size, No Hunner’s lesion-based categorization |
| Bosch      | Certolizumab pegol  | Active=28 (50 years) Placebo=14 (54 years) | Subcutaneous       | O’Leary–Sant ICSP1, GRA, Pelvic Pain, Urgency, Frequency Symptom Scale | Statistically important difference in all outcome measures compared to placebo (week 18) | 18 weeks           | Heterogeneous population, Small sample size, No Hunner’s lesion-based categorization |
| Evans et al | Tanezumab           | Active=34 Placebo=30      | Intravenous        | O’Leary–Sant ICSP1, GRA | No difference compared to placebo regarding ICSP1 Statistically important difference regarding GRA compared to placebo | 6 weeks            | Heterogeneous population, Short follow-up, No Hunner’s lesion-based categorization |
| Wang et al | Fulranumab          | Active=34 (50.6 years) Placebo=30 (46.2 years) | Subcutaneous       | O’Leary–Sant ICSP1, GRA, Pelvic Pain, Urgency, Frequency Symptom Scale | A single dose of 9 mg of fulranumab failed to show analgesic activity | 12 weeks           | Heterogeneous population, Discontinued, No Hunner’s lesion-based categorization |
**Conclusion**

With the exception of the encouraging results regarding the role anti-TNF-α human monoclonal antibodies for the management of PBS/IC, based only on the results of a single study, the rest of the evidence regarding the efficacy of monoclonal antibody therapy failed to report superiority compared to placebo treatment. In summary, the efficacy and safety of monoclonal antibody therapy remain to be further researched in order for it to be included in the potentially promising future treatment options for PBS/IC. Moreover, high-quality studies assessing the potential autoimmunity-based pathophysiological mechanism of PBS/IC, as well as studies providing answers regarding the ideal PBS/IC patient for receiving monoclonal antibody therapy, will certainly be needed.

**Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

**Funding**

No funding was received for the collection, management, analysis, or interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. Imamura M, Scott NW, Wallace SA, et al. Interventions for treating people with symptoms of bladder pain syndrome: a network meta-analysis. *Cochrane Database Syst Rev*. 2020;7:CD013325. doi:10.1002/14651858.CD013325.pub2
2. Ueda T, Hanno PM, Saito R, Meijlink JM, Yoshimura N. Current understanding and future perspectives of interstitial cystitis/bladder pain syndrome. *Int Neurourol J*. 2021;25(2):99–110. doi:10.5213/inj.2142084.042
3. Tung A, Hepp Z, Bansal A, Devine EB. Characterizing health care utilization, direct costs, and comorbidities associated with interstitial cystitis: a retrospective claims analysis. *J Manag Care Spec Pharm*. 2017;23(4):474–482. doi:10.18553/jmcp.2017.23.4.474
4. Hsieh KL, Chin HY, Lo TS, et al. Interstitial cystitis/bladder pain syndrome patient is associated with subsequent increased risks of outpatient visits and hospitalizations: a population-based study. *PLoS One*. 2021;16(9):e0256800. doi:10.1371/journal.pone.0256800
5. Malde S, Palnisani S, Al-Kaisy A, Sahai A. Guideline of guidelines: bladder pain syndrome. *BJU Int*. 2018;122(5):729–743. doi:10.1111/bju.14399
6. Osman NI, Brett DG, Downey AP, Esperto F, Inman RD, Chapple CR. A systematic review of surgical interventions for the treatment of bladder pain syndrome/interstitial cystitis. *Eur Urol Focus*. 2021;7(4):877–885. doi:10.1016/j.euf.2020.02.014
7. Liu S, Zhang C, Peng L, Lu Y, Luo D. Comparative effectiveness and safety of intravesical instillation treatment of interstitial cystitis/bladder pain syndrome: a systematic review and network meta-analysis of randomized controlled trials. *International Urogynecology Journal*. 2021;32(5):1061–1071. doi:10.1007/s00192-020-04990-3
8. Di XP, Luo DY, Jin X, Zhao WY, Li H, Wang KJ. Efficacy and safety comparison of pharmacotherapies for interstitial cystitis and bladder pain syndrome: a systematic review and Bayesian network meta-analysis. *Int Urogynecol J*. 2021;32(5):1129–1141. doi:10.1007/s00192-020-04659-w
9. Pape J, Falconi G, De Mattos Lourenco TR, Doumouchtsis SK, Betschart C. Variations in bladder pain syndrome/interstitial cystitis (IC) definitions, pathogenesis, diagnostics and treatment: a systematic review and evaluation of national and international guidelines. *Int Urogynecol J*. 2019;30(11):1795–1805. doi:10.1007/s00192-019-03970-5
10. Mykoniatis I, Katafigiotis I, Sfoungaristos S, Yutkin V. Immunotherapy options for painful bladder syndrome: what’s the potential? *Expert Opin Biol Ther*. 2017;17(12):1471–1480. doi:10.1080/14712598.2017.1375094
11. Van De Merwe JP, Arendsen HJ. Interstitial cystitis: a review of immunological aspects of the aetiology and pathogenesis, with a hypothesis. *BJU Int*. 2000;85(8):995–999. doi:10.1046/j.1444-410x.2000.06646.x
12. Akiyama Y, Yao JR, Kreder KJ, et al. Autoimmunity to urothelial antigen causes bladder inflammation, pelvic pain, and voiding dysfunction: a novel animal model for Hunner-type interstitial cystitis. *Am J Physiol Renal Physiol*. 2021;320(2):F174–F182. doi:10.1152/ajprenal.00290.2020
13. Yueh HZ, Yang MH, Huang JY, Wei JCC. Risk of autoimmune diseases in patients with interstitial cystitis/bladder pain syndrome: a nationwide population-based study in Taiwan. *Front Med*. 2021;8:747098. doi:10.3389/fmed.2021.747098
14. Warren JW, Wesselsmann U, Morozov V, Langenberg PW. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. *Urology*. 2011;77(3):313–319. doi:10.1016/j.urology.2010.08.059
15. Fan YH, Lin ATL, Lu SH, Chuang YC, Chen KK. Non-bladder conditions in female Taiwanese patients with interstitial cystitis/hypersensitive bladder syndrome. *Int J Urol Off J Jpn Urol Assoc*. 2014;21(8):805–809. doi:10.1111/iju.12456
16. Cheng WM, Fan YH, Lin ATL. Urodynamic characteristics might be variable in bladder pain syndrome/interstitial cystitis patients with different non-bladder co-morbid conditions. *J Chin Med Assoc JCMIA*. 2018;81(3):248–254. doi:10.1016/j.jcma.2017.06.022

17. Christmas TJ. Lymphocyte sub-populations in the bladder wall in normal bladder, bacterial cystitis and interstitial cystitis. *Br J Urol*. 1994;73(5):508–515. doi:10.1111/j.1464-410x.1994.tb07635.x

18. Sant GR, Kemparaj D, Marchand JE, Theoharides TC. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. *Urology*. 2007;69(4 Suppl):34–40. doi:10.1016/j.urology.2006.08.1109

19. Gamper M, Viereck V, Eberhard J, et al. Local immune response in bladder pain syndrome/interstitial cystitis ESSIC type 3C. *Int Urogynecol J*. 2013;24(12):2049–2057. doi:10.1007/s00192-013-2112-0

20. Theoharides TC, Kemparaj D, Sant GR. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. *Urology*. 2001;57(6 Suppl 1):47–55. doi:10.1016/S0090-4295(01)01129-3

21. Peters KM, Diokno AC, Steinert BW. Preliminary study on urinary cytokine levels in interstitial cystitis: does intravesical bacille Calmette-Guérin treat interstitial cystitis by altering the immune profile in the bladder? *Urology*. 1999;54(3):450–453. doi:10.1016/s0090-4295(99)01664-2

22. Ochs RL, Muro Y, Si Y, Ge H, Chan EK, Tan EM. Autoantibodies to DFS 70 kd/Transcription coactivator p57 in atopic dermatitis and other conditions. *J Allergy Clin Immunol*. 2000;105(6 Pt 1):1211–1220. doi:10.1067/mai.2000.107039

23. Lotz M, Villiger P, Hugli T, Kozloj Z, Zurav BL. Interleukin-6 and interstitial cystitis. *J Urol*. 1994;152(3):869–873. doi:10.1016/s0022-5347(17)32594-6

24. Wang F, Jackson MW, Maughan V, et al. Passive transfer of Sjogren’s syndrome IgG produces the pathophysiology of overactive bladder. *Arthritis Rheum*. 2004;50(11):3637–3645. doi:10.1038/ar.2005.2625

25. Hegde SS, Egrem RN. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. *Life Sci*. 1999;64(7–8):419–428. doi:10.1016/s0022-5345(98)00581-5

26. Anderson JB, Parivar F, Lee G, et al. The enigma of interstitial cystitis—an autoimmune disease? *Br J Urol*. 1989;63(1):58–63. doi:10.1111/j.1464-410x.1989.tb05124.x

27. Zayyaz SA, Zhang CQ, Trifillis AL, Hebel JR, Jacobs SC, Warren JW. Urine autoantibodies in interstitial cystitis. *J Urol*. 1997;157(3):1083–1088. doi:10.1016/s0022-5347(01)65146-2

28. Jiang YH, Peng CH, Liu HT, Kuo HC. Increased pro-inflammatory cytokines, C-reactive protein and nerve growth factor expression in serum of patients with interstitial cystitis/bladder pain syndrome. *PLoS One*. 2013;8(10):e76779. doi:10.1371/journal.pone.0076779

29. Felsen D, Frye S, Trimble LA, et al. Inflammatory mediator profile in urine and bladder wash fluid of patients with interstitial cystitis. *J Urol*. 1994;152(1 Pt 1):355–361. doi:10.1016/s0022-5347(17)32739-8

30. Batler RA, Sengupta S, Forrestal SG, Schaeffer AJ, Klumpp DJ. Mast cell activation triggers aurothelial inflammatory response mediated by tumor necrosis factor-alpha. *J Urol*. 2002;168(2):819–825. doi:10.1016/s0022-5347(01)64750-7

31. Boucher W, Kemparaj D, Cao J, Papaliodis D, Theoharides TC. Intravesical suplatast tosilate (IPD-1151T) inhibits experimental bladder inflammation. *J Urol*. 2007;177(3):1186–1190. doi:10.1016/j.juro.2006.10.036

32. Gonzalez RR, Fong T, Belmar N, Saban M, Felsen D, Te A. Modulating bladder neuro-inflammation: RDP58, a novel anti-inflammatory peptide, decreases inflammation and nerve growth factor production in experimental cystitis. *J Urol.* 2005;173(2):630–634. doi:10.1097/01.ju.0000143192.68223.f7

33. Ellis CR, Azenet CE. Adalimumab. In: *StatPearls*. StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557889/. Accessed January 31, 2022.

34. Bosch PC. A randomized, double-blind, placebo controlled trial of Adalimumab for interstitial cystitis/bladder pain syndrome. *J Urol*. 2010;183(5):1853–1858. doi:10.1016/j.juro.2009.12.010

35. Propert KJ, Mayer R, Nickel JC, et al. Followup of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. *J Urol*. 2008;179(2):552–555. doi:10.1016/j.juro.2007.09.035

36. Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyurea in patients with interstitial cystitis. *J Urol*. 2005;173(2):810–815. doi:10.1097/01.ju.0000143192.68223.f7

37. Bourne T, Fossati G, Eddleston A, Vugler A, Nesbitt A. Differential distribution of a PEGylated Fab’ fragment into inflamed versus normal tissue compared with an IgG in arthritis and colitis models. *Ann Rheum Dis*. 2010;69(Suppl 2):A61–A62. doi:10.1136/ard.2010.129650F

38. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn’s disease. *Mod Rheumatol*. 2007;17(2):203–209. doi:10.1097/MOR.0b013e32801a6890

39. Mease P, Deodhar A, Fleischmann R, et al. Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. *RMD Open*. 2015;1(1):e000119. doi:10.1136/rmdopen-2015-000119
47. Dmitrieva N, Shelton D, Rice AS, McMahon SB. The role of nerve growth factor in a model of visceral inflammation. *Neuroscience*. 1997; 78 (2):449–459. doi:10.1016/S0306-4522(96)00575-1
48. Steers WD, Kolbeck S, Creedon D, Tuttle JB. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. *J Clin Invest*. 1991;88(5):1709–1715. doi:10.1172/JCI115488
49. Nickle JC, Mills IW, Crook TJ, Jorga A, Smith MD, Atkinson G, Krieger JN. Tanzeumab Reduces Pain in Women with Interstitial Cystitis/Bladder Pain Syndrome and Patients with Nonurological Associated Somatic Syndromes. *J Urol*. 2016 Apr;195(4 Pt 1):942-8. doi:10.1016/j.juro.2015.10.178
50. Liu HT, Tyagi P, Chancellor MB, Kuo HC. Urinary nerve growth factor but not prostaglandin E2 increases in patients with interstitial cystitis/bladder pain syndrome and detrusor overactivity. *BJU Int*. 2010;106(11):1681–1685. doi:10.1111/j.1464-410X.2009.08851.x
51. Delafoy L, Raymond F, Doherty AM, Eschalier A, Diop L. Role of nerve growth factor in the trinitrobenzene sulfonic acid-induced colonic hypersensitivity. *Pain*. 2003;105(3):489–497. doi:10.1016/S0304-3959(03)00266-5
52. Chang DS, Hsu E, Hottinger DG, Cohen SP. Anti-nerve growth factor in pain management: current evidence. *J Pain Res*. 2016;9:373–383. doi:10.2147/JPR.S89061
53. Schnegelsberg B, Sun TT, Cain G, et al. Overexpression of NGF in mouse urothelium leads to neuronal hyperinnervation, pelvic sensitivity, and changes in urinary bladder function. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(3):R534–547. doi:10.1152/ajpregu.00367.2009
54. Hefti FF, Rosenthal A, Walicke PA, et al. Novel class of pain drugs based on antagonism of NGF. *Trends Pharmacol Sci*. 2006;27(2):85–91. doi:10.1016/j.tips.2005.12.001
55. Abdiche YN, Malashock DS, Pons J. Probing the binding mechanism and affinity of tanezumab, a recombinant humanized anti-NGF monoclonal antibody, using a repertoire of biosensors. *Protein Sci Publ Protein Soc*. 2008;17(8):1326–1335. doi:10.1100/ps.035402.108
56. Brown MT, Murphy FT, Radin DM, Davidson I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled Phase III trial. *J Pain*. 2012;13(8):790–798. doi:10.1016/j.jpain.2012.05.006
57. Katz N, Borenstein DG, Birbara C, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain*. 2011;152(10):2248–2258. doi:10.1016/j.pain.2011.05.003
58. Zhao D, Luo MH, Pan JK, et al. Based on minimal clinically important difference values, a moderate dose of tanezumab may be a better option for treating hip or knee osteoarthritis: a meta-analysis of randomized controlled trials. *Ther Adv Musculoskelet Dis*. 2022;14:1759720X211067639. doi:10.1177/1759720X211067639
59. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. *J Urol*. 2011;185(5):1716–1721. doi:10.1016/j.juro.2010.12.088
60. Nickel JC, Atkinson G, Krieger JN, et al. Preliminary assessment of safety and efficacy of fulranumab as monotherapy in patients with moderate to severe, chronic osteoarthritis of the knee. *Urology*. 2012;80(5):1105–1110. doi:10.1016/j.urology.2012.07.035
61. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanzeumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010;363(16):1521–1531. doi:10.1056/NEJMoa0901510
62. Schnitzer TJ, Ekman EF, Spierings ELH, et al. Efficacy and safety of tanzeumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain. *Ann Rheum Dis*. 2015;74(6):1202–1211. doi:10.1136/annrheumdis-2013-204905
63. Wang H, Romano G, Frustaci ME, et al. Fulranumab for treatment of diabetic peripheral neuropathy pain: a randomized controlled trial. *Neurology*. 2014;83(7):628–637. doi:10.1212/WNL.0000000000000686
64. Sanga P, Katz N, Polverejan E, et al. Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. *Pain*. 2013;154(10):1910–1919. doi:10.1016/j.pain.2013.05.051
65. Mayorga AJ, Wang S, Kelly KM, Thipphawong J. Efficacy and safety of fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: a randomised, placebo- and active-controlled trial. *Int J Clin Pract*. 2016;70(6):493–505. doi:10.1111/ijcp.12807
66. Wang H, Russell LJ, Kelly KM, Wang S, Thipphawong J. Fulranumab in patients with interstitial cystitis/bladder pain syndrome: observations from a randomized, double-blind, placebo-controlled study. *BMC Urol*. 2017;17:2. doi:10.1186/s12894-016-0193-z