

THE EFFECTIVENESS OF TNF- α INHIBITOR THERAPY IN BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To evaluate the effectiveness of TNF- α inhibitor therapy in Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) patients compared to placebo, assessed using Global Response Assessment (GRA). **Material & Methods:** A systematic review and meta-analysis. Subjects were patients with moderate to severe diagnosis of BPS/IC who were given TNF- α inhibitor versus placebo, with the Global Response Assessment (GRA) (patient-reported self-reported BPS/IC treatment response scale). A systematic literature search was carried out on the English databases PubMed/MEDLINE and Science Direct, published until September 2020. Data were extracted independently and assessed the bias and quality of each selected article. **Results:** Initially there were 124 studies. After further selection, 2 RCT studies were included in the criteria for this study. The number of samples obtained was 85 patients. There is 1 study that used 400 mg of certolizumab pegol subcutaneously and 1 study used adalimumab 80 mg subcutaneously and followed by 40 mg subcutaneously for 2 weeks. Both studies had statistically low heterogeneity with $I^2 = 0\%$ ($P = 0.34$), so fixed effect statistical model was used to determine the result. Furthermore, there was no significant difference ($P = 0.32$) between the number of GRA responders from the TNF- α inhibitor and placebo therapy groups, with odds ratio of 1.61 ($CI = 0.65-4.00$). **Conclusion:** TNF- α inhibitor therapy did not increase GRA responders when compared to placebo.

Keywords: Bladder pain syndrome, global response assessment, interstitial cystitis, TNF alpha inhibitor.

ABSTRAK

Tujuan: Mengevaluasi efektivitas terapi TNF- α inhibitor pada pasien Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) dibandingkan dengan placebo, yang dinilai menggunakan Global Response Assessment (GRA). **Bahan & Cara:** Sebuah telaah sistematik dan meta analisis. Subjek penelitian adalah pasien dengan diagnosis BPS/IC sedang sampai berat yang diberikan terapi TNF- α inhibitor versus placebo, serta Global Response Assessment (GRA) (skala respon pengobatan terhadap BPS/IC yang dilaporkan sendiri oleh pasien). Pencarian literatur secara sistematik dilakukan pada database berbahasa inggris PubMed/MEDLINE dan ScienceDirect, yang terpublikasi hingga September 2020. Data diekstraksi secara independen, dan dilakukan penilaian bias serta kualitas studi dari masing-masing artikel yang terpilih. **Hasil:** Pada awalnya didapatkan 124 studi. Setelah seleksi lebih lanjut, didapatkan 2 studi RCT yang masuk dalam kriteria untuk penelitian ini. Jumlah sampel yang didapatkan dari kedua studi tersebut sebanyak 85 pasien. Terdapat 1 studi yang menggunakan terapi certolizumab pegol 400 mg secara subkutan dan 1 studi yang menggunakan adalimumab 80 mg subkutan dan diikuti 40 mg subkutan selama 2 minggu. Kedua studi tersebut memiliki heterogenitas yang rendah secara statistik dengan $I^2 = 0\%$ ($P = 0.34$), sehingga digunakan model statistik fixed effect untuk menentukan hasil. Lebih lanjut, didapatkan perbedaan yang tidak signifikan ($P = 0.32$) antara jumlah GRA responder dari kelompok terapi TNF- α inhibitor dan plasebo, dengan odds ratio 1.61 ($CI = 0.65-4.00$). **Simpulan:** Terapi TNF- α inhibitor tidak dapat meningkatkan GRA responder jika dibandingkan placebo.

Kata Kunci: Bladder pain syndrome, Global Response Assessment, interstitial cystitis, TNF alpha inhibitor.

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INTRODUCTION

Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a chronic pain condition in the bladder

that can be accompanied by pelvic pain and urinary symptoms without clearly identifiable etiology.¹ Its prevalence increases over time, but difficult to determine due to the heterogeneity of its definitions

and nomenclature. Some studies estimate the prevalence of BPS/IC to be around 3-7%.²⁻³ BPS/IC is associated with lower quality of life, which is worsened by the decrease in psychological health, sexual function, sleep quality, work productivity and, limited mobility.⁴

The instrument that is often used to measure the severity of BPS/IC is a self-reported questionnaire. Questionnaires such as the Interstitial Cystitis Symptoms index (ICSI); The Pelvic Pain, Urgency, Frequency (PUF) Symptom scale are some examples of widely used self-reported questionnaires. Apart from the questionnaire, there is also an instrument that is quite easy to use, namely the Global Response Assessment (GRA) which is a treatment response scale for BPS/IC, which is self-reported by patients.

Treatment at BPS/IC is quite challenging due to the lack of clear understanding of the etiology, variations in symptoms between patients, and lack of data regarding the efficacy and safety of the therapy.⁵ The current management principles of BPS/IC are based on biopsychosocial, which is a holistic approach with active patient involvement. Various treatment modalities are possible but none have shown sufficient efficacy in reducing symptoms.⁶

Inflammatory cytokines/chemokines are one of the etiological factors involved in the pathogenesis of BPS/IC.⁷ Tumor necrosis factor- α (TNF- α) plays an important role in inflammation, as well as pain mechanisms in BPS/IC. Thus, it hypothesized that drugs that inhibit TNF may be effective in reducing bladder inflammation and accompanying symptoms.⁸⁻¹⁰ Recently, there are data regarding the use of human monoclonal antibodies that inhibit tumor necrosis factor- α (TNF- α),¹¹⁻¹³ and several studies have evaluated the efficacy and safety of TNF- α inhibitor therapy in BPS/IC. However, no one has ever conducted a meta-analysis in this area.

OBJECTIVE

To evaluate the effectiveness of TNF- α inhibitor therapy in BPS/IC patients compared to placebo, assessed using GRA.

MATERIAL & METHODS

This study used a systematic review and meta-analysis design. Subjects were patients diagnosed with moderate to severe BPS/IC, who

were given TNF- α inhibitor versus placebo therapy. This study uses a quantitative method using The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. In this study, the TNF- α inhibitor therapy variable (Certolizumab, Adalimumab) was determined as the independent variable to be compared with placebo. The dependent variable of this study is the Global Response Assessment (GRA). A systematic search for studies was carried out on the scientific databases of PubMed/MEDLINE and ScienceDirect, published until September 2020. The keywords used are in Table 1.

Study eligibility criteria were defined to sort out the studies included in the meta-analysis. The selection results are based on the criteria of journal articles in English, which are searched systematically using the online database search engine (PubMed, and Science-direct). Search for journal articles from references/bibliography, guidelines, and literature related to this research topic was also carried out. The inclusion and exclusion criteria were presented in Table 2.

Data extraction was carried out independently by all authors. The data extracted included data source, eligibility, method, sample characteristics, intervention, and the results of each study based on a standard form by all reviewers and then cross-checked. Any disagreements were resolved by discussion between the authors. If this author is unable to reach a consensus, other authors are consulted to resolve the dispute and the final decision is made by majority vote. Data extraction was in the form of tabulated data from each selected journal article and codified and analyzed data per research unit to be combined and compared. The data we got was then inputted using Review Manager 5.4 software for analysis.

In this study, an assessment of the research bias and the study quality of each selected journal article was conducted. For RCT studies, this study uses a method from the Cochrane Risk of Bias Tools For Randomized Trials which can classify the research risk by assessing selection bias, performance bias, detection bias, attrition bias, and reporting bias. This study uses the scoring method from The Newcastle-Ottawa Scale (NOS) for observational journal articles that can assess the quality of selection, comparability, and exposure.¹⁴⁻¹⁵

In this study, data from each selected journal article will be presented descriptively and a comparison analysis between variables is carried

Table 1. Keywords used in the database search.

Database	Keywords
PubMed/ MEDLINE	((("tumor necrosis factor alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields]) AND ("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor s"[All Fields])) OR ("certolizumab pegol"[MeSH Terms] OR ("certolizumab"[All Fields] AND "pegol"[All Fields]) OR "certolizumab pegol"[All Fields] OR "certolizumab"[All Fields]) OR ("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields])) AND ("cystitis, interstitial"[MeSH Terms] OR ("cystitis"[All Fields] AND "interstitial"[All Fields]) OR "interstitial cystitis"[All Fields] OR ("bladder"[All Fields] AND "pain"[All Fields] AND "syndrome"[All Fields]) OR "bladder pain syndrome"[All Fields] OR "BPS"[All Fields] OR ("cystitis, interstitial"[MeSH Terms] OR ("cystitis"[All Fields] AND "interstitial"[All Fields]) OR "interstitial cystitis"[All Fields] OR ("interstitial"[All Fields] AND "cystitis"[All Fields])) OR ("infect control"[Journal] OR "infect chemother"[Journal] OR "ic"[All Fields])) Filters applied: Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Multicenter Study, Observational Study, Randomized Controlled Trial. (64)
Science Direct	1. TNF alpha Inhibitor Bladder pain syndrome interstitial cystitis (50) 2. Certolizumab Bladder pain syndrome interstitial cystitis (9) 3. Adalimumab Bladder pain syndrome interstitial cystitis (1)

Table 2. Inclusion and exclusion criteria of the journal article.

Inclusion	Exclusion
Randomized controlled trial, cohort, case-control, or cross-sectional study Studies with 2 or more arms.	Case report, and case series
A study comparing TNF- α inhibitor-type drugs with a placebo.	Studies that use experimental animals as research subjects Laboratory studies conducted in vitro
Patients with a moderate to severe diagnosis of BPS/IC	Review studies such as narrative review, systematic review, and meta-analysis

out. Basic data in the form of the name of the researcher, the year of study, the location of the study, the number of samples, the mean age of the patient, the study design, the type of TNF- α inhibitor drug, and the follow-up were reported as descriptive data. Meta-analysis statistical analysis is used to see the differences between the variables studied. In this study, a forest plot was used to see the differences in each variable for each study. In continuous data, the

analysis used the mean and standard deviation of variables to look for differences in the mean. In the dichotomous data, the number of proportions and the total sample were used to see the difference in odds ratios of each study.

This study uses the Review Manager (RevMan) version 5.4 for Windows as a data analysis processing software. All data obtained will initially be collected in tabulations that are integrated into

one data system. Results were presented using mean difference with odds ratio (OR) and CI 95%. Heterogeneity was analyzed using the I² test and chi-square test. Heterogeneity is significant if I² > 50% or chi-square < 0.1. A random-effect model will be selected if significant heterogeneity is found between studies. The fix-effect model will be selected if no significant heterogeneity is found between studies.

RESULTS

A systematic search for studies was carried out using the PubMed, and Science-Direct database. In the initial selection, there were 124 studies from the combination of the two databases. The flow of this study is briefly described in the PRISMA Flowchart in Figure 1.

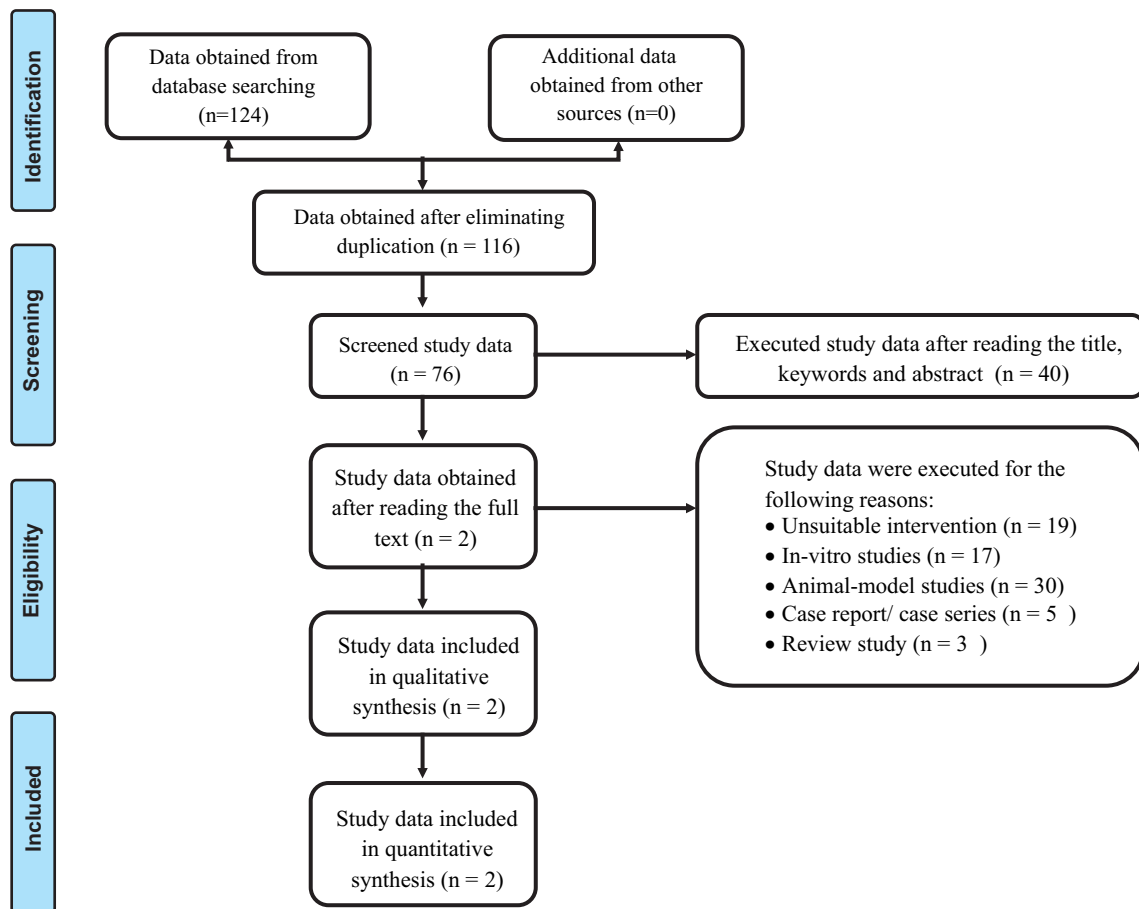


Figure 1. PRISMA flowchart.

Table 3. Basic characteristics of research articles.

Author	Country	Design	Sample	Therapy	Therapy Regimen
Bosch, 2018	United States	RCT	42	Certolizumab P (28) vs Placebo (14)	400 mg subcutaneous
Bosch, 2013	United States	RCT	43	Adalimumab (21) vs Placebo (22)	80 mg subcutaneous, 40 mg subcutaneous per 2 weeks

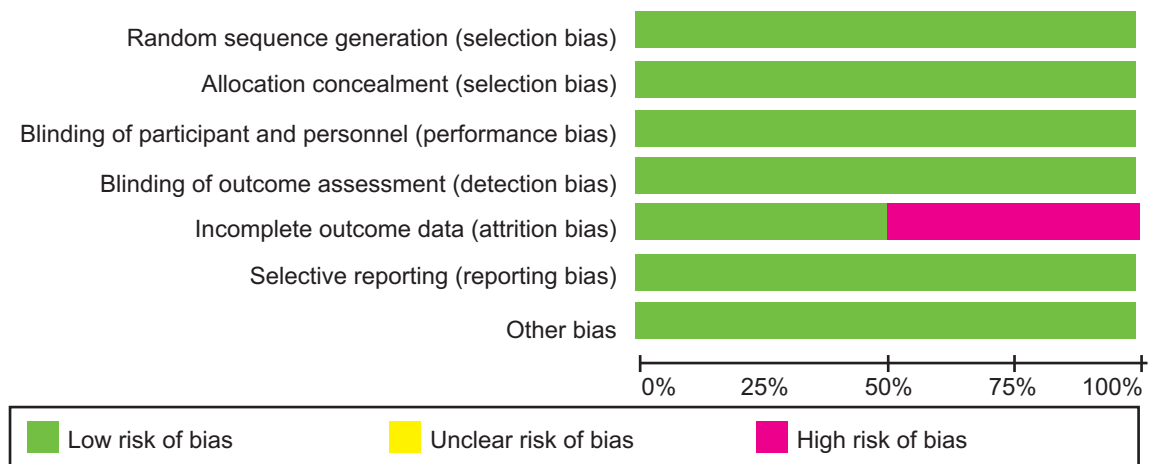


Figure 2. Risk of bias chart.

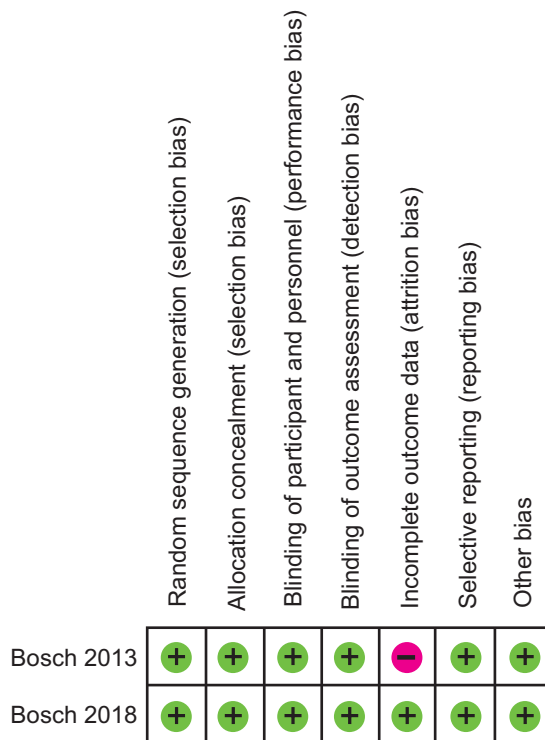


Figure 3. Summary of risk of bias. The green color indicates a low risk of research bias, the red color indicates a high risk of research bias.

Measuring the risk of bias using the method of the Cochrane Risk of Bias Tools for Randomized Trials. In all studies that met the inclusion criteria, randomization of samples into the TNF- α inhibitor and placebo groups was carried out with an adequately described technique. Each study clearly

describes the method of randomization between groups. In the allocation concealment section, there is 1 study that does not describe how clearly it is, but the authors think that the concealment that is carried out is adequate. Both studies carried out the blinding process of research samples and health workers. The two studies did not describe whether the blinding process was carried out on the results of the study, but the authors argued that the absence of a blinding process in the results of the study did not affect the measurement of the research results.

The study conducted by Bosch et al. in 2013 has a high risk of bias for the incompleteness of the research results. The study did not include data on differences in ICSI statistics between study groups. None of the studies had a high risk of reporting bias and all studies were free from other risks of bias.

This study focused on changes in GRA in patients experiencing BPS/IC who were given TNF- α inhibitor therapy compared to placebo. GRA responders are patients who experience moderate and large increases in GRA. In a study conducted by Bosch et al in 2018, 12 patients (42.8%) were found in the TNF- α inhibitor therapy group who were GRA responders, while only 3 patients (21.8%) were from the placebo group. In a study using adalimumab as a TNF- α inhibitor, 11 patients (52.3%) were GRA responders. However, in the placebo group, a total of 11 patients (50.0%) were also GRA responders.

In this study, a Forest plot analysis was conducted to determine the significance and heterogeneity of differences in GRA responders between the TNF- α inhibitor and placebo groups. The combination of the two studies had statistically low heterogeneity with $I^2 = 0\%$ ($P = 0.34$).

Table 4. The number of GRA responders from each group.

Author	Sample	GRA responder	
		TNF-α inhibitor	Placebo
Bosch, 2018	Certolizumab P (28) vs Placebo (14)	12 (42.8%)	3 (21.8%)
Bosch, 2013	Adalimumab (21) vs Placebo (22)	11 (52.3%)	11 (50.0%)

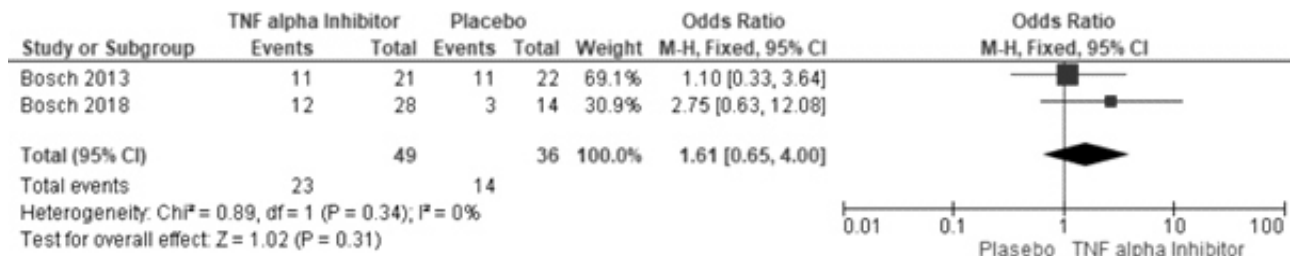


Figure 4. Forest plot of the differences in GRA responder between TNF-α inhibitor and placebo.

Therefore, a fixed effect statistical model is used to determine the results of the study. Furthermore, in this study, there was no significant difference ($P = 0.32$) between the number of GRA responders from the TNF-α inhibitor and placebo therapy group with an odds ratio of 1.61 (CI = 0.65-4.00).

DISCUSSION

Interstitial cystitis (IC), painful bladder syndrome (PBS), and bladder pain syndrome (BPS) are chronic conditions of the bladder, whose definitions are still evolving, with a lack of consensus regarding the etiology, diagnosis, and treatment of these conditions. The International Continence Society (ICS) changed the terminology to PBS and defines suprapubic pain conditions associated with bladder filling with urinary frequency unrelated to other conditions.¹⁶ ICS introduced the terms BPS and IC can be used interchangeably.¹⁷⁻¹⁸

Patients with BPS/IC have a low quality of life accompanied by pain, sleep disturbances, depression, anxiety, and sexual dysfunction. There are several treatments such as analgesics, heparin, and lidocaine intravesical instillation that have been used as standard therapy for BPS/IC. However, only 50% of patients feel that their condition is improving.¹⁹

Previous studies suggest that pro-inflammatory cytokines such as TNF-α are involved in the pathophysiology of BPS/IC. TNF-α is a

pleiotropic cytokine associated with various autoimmune diseases such as Crohn's disease and psoriasis. TNF-α is a major component of compounds secreted by mast cells that are involved in several bladder diseases such as bacterial infections, carcinoma, and also BPS/IC. After the release of TNF-α, apoptosis and endothelial lesions occur. This is evidenced in studies using mice, where overexpression of TNF-α can increase symptoms of pelvic pain, urinary dysfunction, and urothelial lesions.²⁰⁻²¹

Several monoclonal antibody drugs have been developed in recent decades. One of the monoclonal antibodies that have been developed is TNF-α inhibitor. Examples of TNF-α inhibitors are adalimumab, infliximab, certolizumab, and golimumab. Based on a systematic study search, there were only 2 studies with 2 types of TNF-α inhibitor drugs, namely adalimumab and certolizumab. Both drugs have been approved by the FDA to treat autoimmune diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease.²⁰

In 2013, Bosch conducted a phase III clinical trial, using a randomized, double-blind, placebo-controlled, and proof of concept study. Patients with BPS/IC were randomized to receive adalimumab therapy with an initial dose of 80 mg subcutaneously followed by 40 mg every 2 weeks or subcutaneous placebo therapy for 12 weeks, of which 21 patients received adalimumab and 22 patients received placebo therapy. In patients who received adalimumab therapy, there was a

significant improvement based on the O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes ($p = 0.0002$), Interstitial Cystitis Symptom Index ($p = 0.0011$), Interstitial Cystitis Problem Index ($p = 0.0002$), and Pelvic Pain, Urgency, Frequency Symptom Scale ($p = 0.0017$) at 12 weeks compared to baseline. At 12th week, 11 of 21 patients (53%) reported an improvement in global response assessment of 50% or more ($p = 0.0001$). Meanwhile, there was no statistically significant difference in symptom improvement between patients receiving adalimumab therapy and placebo.¹⁹

In 2018, Bosch conducted a randomized, double-blind, placebo-controlled pilot study that compared certolizumab therapy with placebo. Study samples were randomized to receive either certolizumab or placebo therapy in 2:1 ratio (28 patients received certolizumab therapy and 14 patients received placebo therapy). Giving certolizumab pegol 400 mg subcutaneously at weeks 0, 2, 4, and 8.

The results of GRA analysis at 2nd week did not show a statistically significant difference between the certolizumab and placebo groups. However, at 18th week, there was a significant improvement in the GRA of patients receiving pegol certolizumab therapy versus placebo in pain symptoms (odds ratio [OR] = 17.3, $p = 0.002$), urgency (OR = 9.92, $p = 0.02$), and overall symptoms (OR = 15.0, $p = 0.006$). At week 18, there was a statistically significant improvement between certolizumab pegol therapy versus placebo in the change in ICSI, that was -3.6 (95% confidence interval [CI]: -6.9 to -0.29, $p = 0.03$), ICPI of -3.0 (95% CI: -6.1 to 0.12, $p = 0.042$), the pain scale was -2.0 (95% CI: -3.9 to -0.15, $p = 0.02$), and the urgency scale was -1.7 (95% CI: -3.5 to 0.06, $p = 0.03$). There was a significant difference between certolizumab pegol and placebo in the reduction of pain symptoms above 30% at 18th week (OR = 13.0, $p = 0.02$). For better results, this study suggests a larger, longer duration, and multicentric study to allow for phenotypic categorization of patients.¹²

The inhibition of the TNF- α cytokine released by mast cells is the key to the hypothesis of this study. From the two studies, it was found that the number of GRA responders was not statistically significant between the groups receiving TNF- α inhibitor therapy when compared to the group given only placebo. However, the forest plot results obtained showed a trend towards TNF- α inhibitor therapy in the number of GRA responders (OR =

1.61, 95% CI = 0.65-4.00), especially certolizumab drugs. The results of this study have low statistical heterogeneity ($P = 0.34$, $I^2 = 0\%$), therefore statistical tests can be performed using a fixed effect model.

In a study using TNF- α inhibitor therapy for autoimmune Crohn's disease, significant results were obtained in the TNF- α inhibitor group. It can be supported that the cytokines that play a role in BPS/IC disease are not only TNF- α . Several other cytokines play a role in the pathophysiological process of BPS/IC such as IL2, IL3, Nerve growth factor (NGF), and many others that are still not clearly detected.²²

Research using the NGF inhibitor-Tanezumab therapy gave significant results, but not the NGF inhibitor-fulranumab therapy. There have been several previous studies examining the use of humanized anti-NGF monoclonal antibodies in patients with BPS/IC. A study by Evans et al., a randomized, double-blind, placebo-controlled, phase 2 clinical study, in patients with IC, compared the use of tanezumab to placebo. The study consisted of 64 samples, 34 samples received tanezumab, while 30 patients received placebo therapy. Samples received a single dose of 200 μ g/kg intravenous tanezumab. At week 6, tanezumab therapy showed a significant reduction in pain scores compared with placebo. Overall, 57% of patients receiving tanezumab therapy and 35% of patients receiving placebo therapy experienced a reduction in pain scores of 30% or more. Meanwhile, 36% of patients receiving tanezumab therapy and 9% of patients receiving placebo therapy experienced a reduction in pain scores by 50% or more. Meanwhile, the GRA assessment at 6th week showed that patients who received tanezumab therapy experienced greater symptom improvement than patients who received placebo (OR 5.1).²³

A study by Wang et al., using a randomized, double-blind, placebo-controlled, multicenter study, compared fulranumab therapy with placebo in BPS/IC patients. The sample in this study was 31 patients, of which 17 patients received placebo, and 14 patients received fulranumab 9 mg subcutaneously at weeks 1, 5, and 9. In this study, there was no statistically significant difference between fulranumab and placebo in primary efficacy endpoint (Average Pain Intensity Score). However, there is an upward trend in GRA. Five patients (35.7%) in the fulranumab group and 4 (23.5%) patients in the placebo group reported GRA scores "there was a large improvement" or "there was an

adequate improvement", 5 patients in each group (35.7% and 29.4%, respectively) reported a GRA score "there was minimal improvement, and 4 patients (28.5%) and 8 patients (47.1%) in each group reported "no change", "minimum", or "deterioration" of the GRA score.¹³

This study has several limitations, including the total number of studies obtained in this study was only 2 RCTs. There is 1 study with a high risk of research bias in terms of incomplete outcome data, but this study did not examine this incomplete outcome. Each study has a different type of drug even though it is still in one drug class.

CONCLUSION

In conclusion, TNF- α inhibitor therapy did not increase GRA responders when compared to placebo. Further research is needed regarding TNF- α inhibitor therapy against BPS/IC with a larger sample, with in-depth analysis of the role of the cytokine in BPS/IC.

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