



Efficacy Study of New Drug Mercureid (MSC-428) in Anti-TNF α Therapy for Chronic Prostatitis

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Abstract

The prevalence of prostatitis ranges from 2% to 9% in the total male population. It has a significant negative impact on the quality of life, comparable to such diseases as diabetes, Crohn's disease and myocardial infarction.

As meta-analysis in Medline, PubMed, Cochrane Register of Controlled Trials (conducted from May 1990 to July 2012) has indicated, there is a significant positive connection between prostatitis and prostate cancer. And chronic inflammation is connected with a high risk of cancer compared with acute inflammation.

The analysis of the conducted research has shown that the use of only standard criteria for the treatment of chronic prostatitis does not satisfy the current knowledge about the role of chronic inflammation as a predictor of the development of hyperplasia or cancer.

All this predetermined the relevance of the clinical study of innovative molecules MSC-428 (trade name Mercureid) approved by the State Pharmacological Center of the Ministry of Health of Ukraine. This study was conducted as a randomized, comparative placebo-controlled in 130 patients who had chronic prostatitis. In addition to the standard criteria for evaluating the therapy efficacy, the modern immune biomarkers such as TNF α and S-IgA were applied.

The clinical study has shown the efficacy of MSC-428 in anti-TNF therapy – 74%. The unique stereochemical parameters of MSC-428 molecules made it possible to reduce the overexpression of both TNF α and S-IgA, as increased levels of S-IgA and TNF α form a pathogenetic link between inflammation and carcinogenesis.

The novelty of the work is the following. The detailed analysis of the present-day scientific works proved the absence of information about the branded drugs of anti-TNF α therapy that could reduce a high level of S-IgA. Besides, in contrast to the intravenous or subcutaneous injections, which are required for the delivery of active molecules (mAb), the sublingual administration of MSC-428 molecules was studied as a simpler and safer method of conducting anti-TNF therapy.

Thus, we can state that the therapeutic use of MSC-428 (Mercureid) is an important contribution to the further development of anti-TNF therapy, which is aimed at reducing the risk of developing benign hyperplasia and cancer.

Keywords: Drug; Mercureid; TNF α ; Therapy

Introduction

The prevalence of prostatitis ranges from 2% to 9% in the total male population. It has a significant negative impact on the quality of life, comparable to such diseases as diabetes, Crohn's disease and myocardial infarction.

As meta-analysis in Medline, PubMed, Cochrane Register of Controlled Trials (conducted from May 1990 to July 2012) [1] has indicated, there is a significant positive connection between prostatitis and prostate cancer. And chronic inflammation is connected with a high risk of cancer compared with acute inflammation [2].

The high prevalence of prostatitis may contribute to prostate carcinogenesis, which is the most common malignant tumor among elderly men in the United States, and the second-leading cause of death for men [3].

More than 2 million people suffer from prostatitis in the United States every year [4]. Moreover, many researchers and urologists believe that the frequency of asymptomatic prostatitis appearance can be much higher than symptomatic prostatitis [5].

Currently, inflammation is present in approximately 17% of all cancer cases [6]. The German researcher Rudolf Virchow was the first to discover a positive connection between inflammation and cancer in 1863 [8]. After that, epidemiological and biological studies focused on the function of inflammation in order to find out the evidence of this causal relationship. Epidemiological studies, including control and cohort studies have concluded that inflammation is closely connected with several types of cancer, including intestines, stomach, esophagus, prostate gland, etc. [9-11].

The studies have shown that active oxygen and nitrogen radicals, which are produced by inflammatory tissue, increase the risk of cancer development, suppressing antitumor activity and stimulating carcinogenesis [12,13]. New genetic data indicate that transcription factors, NF-kB and STAT3, play a great role in the association between inflammation and cancer [14,15].

Thus, there is sound evidence relating the role of prostatitis in the development of prostate cancer. It is logical to prevent prostate cancer by immunopathogenetic therapy of chronic prostatitis [16-19].

All this predetermined the relevance of the clinical study of innovative molecules MSC-428 (trade name Mercureid) approved by the State Pharmacological Center of the Ministry of Health of Ukraine. This study was conducted as a randomized, comparative placebo-controlled in 130 patients who had chronic prostatitis.

The authors conducted a meta-analysis aimed to review all trials reporting on therapeutic intervention for CP using the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI I). They searched Medline, PubMed, the Cochrane Register of Controlled Trials, CINAHL, ClinicalTrials.gov, and the NIDDK website which provide information in different publication languages or study type restrictions. It has been found out that chronic prostatitis was treated with several different interventions but there was a limited success. The results of this meta-analysis have reflected the current inability to manage CP effectively [20]. Thus, the clinicians and researchers must consider placebo effect and treatment efficacy and design studies creatively so to have an opportunity to elucidate more fully the etiology and role of therapeutic intervention in CP.

Therefore, in addition to the standard criteria for evaluating the therapy efficacy (complete blood count, blood biochemistry,

ultrasound, bacterial urine culture, NIH-CPSI questionnaire, the International Prostate Symptom Score (IPSS), Quality of life questionnaire (QoL)), the modern immune biomarkers such as S-IgA and TNF α were applied in prostate secretion [21].

The prostate is a part of the common mucosal immune system, CMIS [22,23]. Chronic prostatitis, benign hyperplasia, and prostate cancer are connected with increased secretion of IgA in the prostatic fluid. This indicator correlates with the activity of pathological development [24].

The new research methodology turned out to be much better comparing to many existing research studies, as it provides immunological evidence in the form of reduced expression of the pro-inflammatory cytokine TNF α and S-IgA, that demonstrates the possibility of immunopathogenetic prevention of cancer development [25-29].

Thus, a new understanding of the ways of treatment of chronic inflammation, aimed at reducing the level of pro-inflammatory cytokine TNF α and S-IgA, as predictors of cancer and prostate hyperplasia, is formed.

As this study has shown, the application of drug Mercureid causes in patients:

1. A significant decrease in the level of pro-inflammatory cytokine TNF α in the prostate gland secret, $p < 0,05$.
2. The decrease in the level of S-IgA in the prostate secretion in Mercureid group was more intense compared to the placebo group, $p < 0,05$.
3. The dynamics of the improvement in the indicators of NIH-CPSI, IPSS, QoL questionnaires were more obvious in Mercureid group.
4. The therapeutic efficacy when taking Mercureid was 74%, taking a placebo was 44%.
5. The patients tolerated the action of drug Mercureid reasonably well. Side effects and negative symptoms in this drug application during the treatment were not registered.
6. The duration of the disease course without recurrence. In the group of patients, who took Mercureid, 36% of men experienced exacerbation, in the placebo group, 69% of patients had exacerbation. The follow-up observation period was 6 months after the treatment.
7. The sublingual pathway for the delivery of MSC-428 molecules, TNF α antagonists, is potentially safer, more convenient and simpler than a parenteral one.

It should be noted that the detailed analysis of the present-day scientific works proved the absence of information about the branded drugs of anti-TNF α therapy that could reduce a high level of S-IgA.

The unique stereochemical parameters of MSC-428 molecules make it possible to act both on the systemic and on the local levels

– to reduce the overexpression of TNF α and normalize secretion of S-IgA, as an important factor of mucosal immunity.

Thus, the therapeutic application of MSC-428 (trade name Mercureid) has the potential to reduce the risk of developing benign hyperplasia, prostate cancer and cancer of the other organs [7-15].

This research makes an important contribution to the existing scientific literature for better understanding the nature of the development of immune-inflammatory diseases and the possibilities of modern therapy to treat with the help of innovative molecules MSC-428.

Patients recruitment

The volunteers for this study were recruited from the patients who had an outpatient treatment at the clinic of the Department of Clinical Immunology and Allergology with a course of children's clinical immunology at Bogomolets National Medical University and at the department of sexopathology and andrology, Institute of Urology, Academy of Medical Sciences of Ukraine, Kiev.

All patients included in the study were randomly assigned to the first group (50 people) and the second group (50 people). The patients of the first group received the new medication – trade name Mercureid – sublingually in granules; the patients of the second group – placebo – took the medication also sublingually in the granules, which were similar in shape and colour to medication Mercureid.

Sublingual administration of drug molecules is a global priority, both to eliminate the risk of misuse and unsafe use of needles and to simplify drug injection procedures [30].

For proving simplicity of anti-TNF therapy, mucous pathways are the most important ones [31]. As the main route of administration of anti-TNF therapy molecules, which mainly consists of specific monoclonal antibodies, is intravenous or subcutaneous, that is connected with significant risks of infection, it requires special equipment, medical staff, storage conditions. All the above-mentioned things certainly impose restrictions on treatment procedures.

An alternative variant could be the sublingual administration of MSC-428 molecules - TNF α receptor antagonists, through mucous membranes. This study demonstrated the potential of the sublingual route for molecule administration, which caused both a systemic immune response and a mucosal immunity response (T and B cells) [32].

- The control group consisted of 30 healthy donors.
- The treatment lasted 28 days.
- A comparative placebo-controlled method was used in the study.
- A randomization list of the drugs needed for 100 patients was compiled. The study drugs (Mercureid/placebo) were encrypted in this list.

- The numbers of the randomization code were labeled on the study drugs.
- The researcher assigned the numbers of the randomization list to the patients who were included in the study, and gave the patient a package of the medication corresponding to the randomization number.
- The patient's randomization number was entered into the individual registration form.

The patients were examined by means of the following methods

- Symptom Index of Chronic Prostatitis (NIH-CPSI Questionnaire, 1999);
- Registration of patient's subjective complaints: the index of symptoms in prostate diseases and the quality of life questionnaire (IPSS and QoL);
- Digital rectal examination of the prostate gland;
- Ultrasound of the prostate and bladder;
- Determination of S-IgA, TNF α in the prostate secretion;
- Complete blood count, urine;
- Biochemical blood examination.

The research group included the patients who gave a written informed consent for participation in a research study. This consent corresponded to the inclusion/exclusion criteria described in the clinical study protocol.

Drug safety

The safety of the drug was evaluated on the basis of clinical, instrumental, laboratory examination methods, as well as subjective sensations reported by the patient to the doctor. The frequency of appearance and nature of side reactions/adverse events were taken into account.

Conditions for early termination of the study

The study should have been interrupted in the case of:

- The occurrence of severe side effects in most patients in the first days or hours of the test;
- Impossibility to fulfill the conditions of the clinical study protocol;
- By the decision of the customer.

The researcher was to inform the customer, the department of coordination and control of clinical trials of the State Pharmacological Center of Ministry of Health of Ukraine and the Central Ethics Commission about the suspension of the test.

Patient selection

Criteria for patients' inclusion in the study:

- Men;
- Age up to 70 years old;
- Diagnosis: chronic prostatitis;

- The number of leukocytes in the secret of the prostate gland ≥ 15 in the optical “field of view” or the presence of leukocytes in the 2nd and 3rd portion of urine obtained after massage of the prostate gland;
- Content **tnf α above normal in prostate secretion**;
- Presence of bacteria growth in prostate secretion culture;
- Informed written consent of the patient for participation in the study;
- Patient’s ability to cooperate adequately during the research process.

Exclusion criteria

- Volume of residual urine more than 150 ml;
- Q max <5 ml/s;
- Known hypersensitivity to the drug components;
- Patient’s inability to refuse to take alcohol during the study period;
- Presence of concomitant decompensated diseases or acute conditions that can significantly affect the results of the study;
- Neurogenic bladder dysfunction;
- Patients after surgery or other invasive interventions on the prostate;
- Patients with an increased risk of acute urinary retention;
- Intake non-recommended drugs one month before and during the study;
- Participation in any other clinical study;
- Patient’s inability to cooperate adequately;
- Patient’s refusal to give a written consent to participate in the study.

Efficacy evaluation

Efficacy criteria

- The degree of reduction of the main clinical manifestations of chronic prostatitis according to the index of symptoms of chronic prostatitis (questionnaire NIH-CP-SI, 1999) and characteristic complaints from the patient (questionnaire IPSS and QOL);
- The degree of normalization of S-IgA and TNF α content in the secret of the prostate gland.

Ethical aspects of research

- This clinical study was conducted in accordance with the Law of Ukraine “On Medicines” and the ethical principles of Helsinki Declaration.
- This study was initiated after the approval of the clinical study protocol by the Ethics Commission of the Ministry of Health of Ukraine.
- The patients who were supposed to be potential participants in the study were informed about the nature of the clinical study, the study drug, as well as the potential risk

connected with taking the drug. Every patient was provided with the written information about the study drug and the research being conducted, contained in the “Information for the patient”.

- All the patients included in the research group gave a written consent to participate in the study.

Study of drug Mercureid efficacy according to the dynamics of changes in the indicators of the muscular immunity

- Taking into account the association of the prostate gland with the reproductive tract, its topography and the presence of subepithelial (stromal) IgA-rich cells, the human prostate gland is a part of the common immune system of the mucous membranes (CMIS) [33].
- Changes in the concentration of S-IgA (Fowler JE, Mariano M., 1984) and the local production of pro-inflammatory cytokine TNF α in prostate secretion can serve as an important criterion not only of the dynamics of the inflammatory process, but also as an indication of the therapy efficacy [34].
- Meta-analysis shows that there is a significant positive connection between prostatitis and prostate cancer.
- This finding is in accordance with many previous biological and epidemiological studies (Ohshima H, Bartsch H (1994), Macarthur M, Hold GL (2004), Ritchie JM., *et al.* (2003), which show that inflammatory mediators [35] may contribute to carcinogenesis of the prostate through multiple signaling pathways: inhibition of apoptosis, stimulation of cell proliferation and death-inducing tumor suppressor gene [36]. This led to the aim of the immunological research.
- The aim was to study the content of serum immunoglobulin A (S-IgA) and TNF α as the main mediators of inflammation and the risk of developing prostate cancer in patients with chronic prostatitis before and after the therapy with Mercureid [37]. Immunological studies were conducted before and after the treatment of 50 patients who took the drug Mercureid in combination with traditional therapy for chronic prostatitis and the treatment of 50 patients who took placebo while undergoing traditional treatment. The control group consisted of 30 healthy donors.
- The main selection criteria for patients with chronic prostatitis in the research groups were the following: the initial increase in the concentration of TNF α in the gland secretion and impaired S-IgA synthesis [38]. On the basis of the dynamics of these indicators normalization, the immunological efficacy of study drug Mercureid was evaluated [39].
- The content of S-IgA in the prostate secretion was determined by means of radial immunodiffusion using monospecific antisera provided by Research Institute for Epidemiology and Microbiology named after N. Gamaleya (Moscow) and SEROTEC (England).

- The level of tumor-quotient factor (TNF α) in the prostate secretion was determined by means of enzyme-linked immunosorbent assay (ELISA). To determine the concentration of the cytokine, a commercial test kit supplied by DIACLONE (France) was used.
- To assess the reliability of differences in indicators in the dynamics of the patients' treatment (before and after the treatment), the nonparametric Mann - Whitney U-test was used.

The study of TNF α in the prostate gland secretion of patients with chronic prostatitis

The indicators of TNF α concentration in the prostate gland secretion of 50 patients with chronic prostatitis who received complex therapy and placebo and 50 patients who received Mercureid during the complex therapy are presented in Table 1.

Term of medical examination	Indicator TNF α , pg/ml		
	Before treatment M \pm m	14 day M \pm m	28 day M \pm m
Mercureid (n-50)	68,78 \pm 2,59	51,43 \pm 2,39	29,89 \pm 1,8*
Placebo (n-50)	63,16 \pm 2,04	57,26 \pm 1,69	49,05 \pm 1,42*
Control group (n-30), M \pm m	19,1 \pm 1,09		

Table 1: Indicators of TNF α in prostate gland secretion of patients with chronic prostatitis.

* p<0,05

As Table 1 shows, before the treatment, all patients with chronic prostatitis experienced a significant increase in the level of TNF α in the prostate secretion compared with the control group.

On the 14th day of the study, there was a tendency for a more intense decrease in the concentration of TNF α in the prostate secretion in Mercureid group.

After 28 days of the complex therapy in the group of patients who received drug Mercureid, TNF α concentrations in the prostate secretion significantly decreased, however did not reach the levels of TNF α concentration in the control group.

In the group of patients who received placebo, the level of TNF α in the prostate secretion was decreasing too but it didn't reach the norm and remained significantly higher than in Mercureid group.

The comparison of TNF α concentration indicators in prostate secretion is presented in Figure 1.

Figure 1 demonstrates that the dynamics of decrease of TNF α concentration in the group of patients who received Mercureid was more obvious after the therapy that indicates the ability of molecules to make a systemic anti-inflammatory effect by inhibiting TNF α .

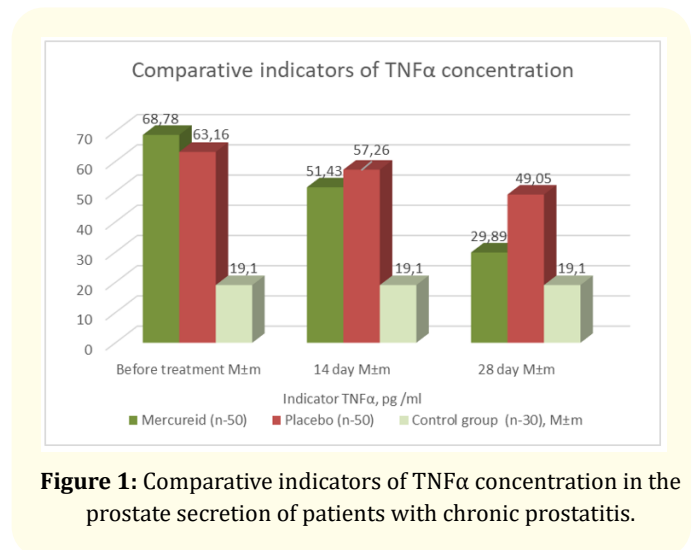


Figure 1: Comparative indicators of TNF α concentration in the prostate secretion of patients with chronic prostatitis.

It should be noted that this fact is confirmed by the number of patients who have a significant positive dynamics in decreasing TNF α indicators in the prostate gland secretion (>30%-50% from the initial state before the treatment) on the 28th day of the study.

As it turned out, the number of such patients in the group who received Mercureid (32 people - 64%) was significantly higher than the patients who received placebo (15 people - 30%) (Mann - Whitney U-test).

The study of S-IgA in the prostate gland secretion of patients with chronic prostatitis

This study confirmed the activation of local immunity in the prostate gland secretion in the groups of patients with chronic prostatitis as a breach of the synthesis of secretory immunoglobulin A (S-IgA) [40].

Table 2 demonstrates that on the 14th day of treatment, the level of secretory IgA in both groups did not decrease significantly. After 28 days of complex therapy in the groups of patients who took drug Mercureid, the level of secretory IgA decreased more intensively. S-IgA concentration in the placebo group also decreased but nevertheless it remained high compared with Mercureid group [41].

Term of medical examination	Indicator S-IgA, g/l		
	Before treatment M \pm m	14 day M \pm m	28 day M \pm m
Mercureid (n-50)	3,01 \pm 0,07	2,15 \pm 0,08	0,87 \pm 0,05*
Placebo (n-50)	2,90 \pm 0,09	2,70 \pm 0,09	2,36 \pm 0,1*
Control group (n-30), M \pm m	0,31 \pm 0,08		

Table 2: The indicators of S-IgA in the prostate gland secretion in patients with chronic prostatitis.

* - p<0,05

The comparison of dynamics of S-IgA concentration indicators in both groups is presented in Figure 2.

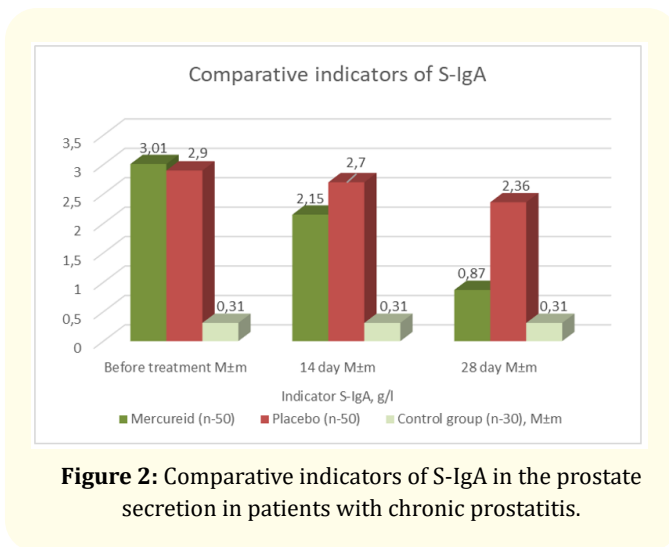


Figure 2: Comparative indicators of S-IgA in the prostate secretion in patients with chronic prostatitis.

As shown in Figure 2, when comparing S-IgA indicators in the prostate gland secretion in patients with chronic prostatitis on the 28th day of therapy, a positive dynamics in the decrease of S-IgA indicators in patients who took Mercureid was observed.

As in the case of TNF α , an individual analysis of the results showed that the number of patients with a significant positive dynamics in the decrease (>30% - 50% from the initial state) of S-IgA indicators in the prostate gland secretion on the 28th day of therapy was also significantly higher in the group of patients who took drug Mercureid (37 people - 74%) than in the group of patients who took placebo (16 people - 32%) (Mann - Whitney U-test).

According to the analysis of the data obtained from the immunological examination of the patients with chronic prostatitis, which is a predictor of prostate cancer [42], it is possible to conclude that drug Mercureid, which was administered to patients sublingually, has a systemic anti-inflammatory effect on mucosal immunity [43] exerting also oncoprotective effect, connected with a decrease in TNF α synthesis and normalization of S-IgA secretion [44].

Conclusions

1. A significant decrease in the level of pro-inflammatory cytokine TNF α , pg/ml in the prostate gland secret from 68.78 to 29.89 in Mercureid group and from 63.16 to 49.05 in the placebo group, $p < 0,05$.
2. Decrease in S-IgA level, g/l in the prostate secretion from 3.01 to 0.87 in Mercureid group. The decrease in the placebo group was from 2.90 to 2.36 that is less intensive compared to Mercureid group, $p < 0,05$.
3. When analyzing the research data, we can come to the conclusion about a more obvious relief of pain, dysuria and intoxication syndromes in chronic prostatitis (CP) and, as a result, an improvement in the quality of

patients' life (according to the NIH-CPSI questionnaire, the International Prostate Symptom Score (IPSS), Quality of life questionnaire (QoL) in Mercureid group compared with placebo group.

4. The study indicates therapeutic efficacy - 74% when applying drug Mercureid compared with placebo (therapeutic efficacy - 44%) in the treatment of patients.
5. The patients tolerated the action of drug Mercureid reasonably well. Side effects and negative symptoms in this drug application during the treatment were not registered.
6. As for the duration of the disease course without recurrence, in the group of patients, who took Mercureid, 36% of men experienced exacerbation, in the placebo group, 69% of patients had exacerbation. The follow-up was 6 months after the treatment.
7. The non-invasive, sublingual route for delivery of MSC-428 molecules, TNF α antagonists, is potentially safer, more convenient, simpler than intravenous or subcutaneous.

A clinical study showed the efficacy of MSC-428 (trade name Mercureid) in anti-TNF therapy. Drug Mercureid has a potentially oncoprotective effect connected with the decreased expression of the pro-inflammatory cytokine TNF α and normalization of S-IgA secretion - key inflammatory mediators that promote carcinogenesis of the prostate gland through multiple signaling pathways: inhibition of apoptosis, stimulation of cell proliferation and inhibition of apoptosis, stimulation of cell proliferation and death-inducing tumor suppressor gene.

It should be noted that no data indicating that anti-cytokine therapy drugs are also able to reduce the high level of S-IgA have been found in the available scientific literature.

Thus, the widespread clinical application of MSC-428 (trade name Mercureid) has the potential to reduce the risk of developing cancer not only of the prostate gland, but also of the other organs.

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