G. Plăcintă

CLINICAL AND LABORATORY EFFICACY OF INTERLEUKIN-5 *LOW DOSE* AND CITOMIX IN PATIENTS WITH LARVAL TOXOCAROSIS

SUMMARY

Toxocarosis is one zooanthroponosis with a severe, long-acting and recidivating evolution, with a large diversity of clinical manifestations in dependence of larva migrans localization, activity degree and *larvae* number, with serious consequences.

- Larvae have a mechanic, traumatic, infectious and toxicoallergic activity on tissues.
Reaction of immune complexes is resposable for the apparition of fever, urticaria, and generalised limphadenopathy.
A particularity of this disease is the very various symptomatology, from asymptomatic forms (the most frequent) to extremely severe forms.

- In this study we aimed to determine the clinical and laboratory efficacy of PRM medicines – Interleukin 5 *low dose* in association with Citomix in patients with various manifestation forms of larval toxocarosis to whom previous standard antihelmintic treatment courses were no effective, clinically and laboratory.
- The present study demonstrated the superior clinical therapeutic and laboratory efficacy of Citomix and Interleukine-5 *low dose* in patients with larval toxocarosis in comparison with antecedent therapeutic courses with drugs belonging to the group of *bensimidasol*, which are utilized in the intra- and extra intestinal nematodosis treatment, including toxocarosis.
- The treatment with Citomix and Interleukin-5 *low dose* may be recommended to patients suffering from larval toxocarosis, especially in forms with long-lasting evolutions, with failure in "classic" therapy, accompanied by different degrees of immunodeficiency.

KEY WORDS

TOXOCARIOSIS, *LOW DOSE*, CITOMIX, INTERLEUKIN-5 *LOW DOSE*

From: http://158.83.1.40/Buckelew/images/Toxocara%20canis%20egg%20good.jpg

Larval toxocarosis is a very frequent parasitosis registered in recent years.
This illness invokes diagnostic and, especially, therapeutic problems.

– Toxocarosis is one zooanthroponosis with a severe, long-acting and recidivating evolution, with a large diversity of clinical manifestations in dependence of *larva migrans* localization, activity degree and larvae number, with serious consequences.

The results of blood donors and young men under 18 years of age serologic examinations by ELISA test demonstrated a high degree spread of the parasitosis determined by larva **S_2 *Toxocara canis*** in population seeming healthy in Republic of Moldova (58,6%).

Toxocara infestation was constated to the majority of patients with various diseases accompanied by blood **hypereosinophilia** too.
Thus, the blood hypereosinophilia presence with various redundant values was determined in **1525** cases (12,1%) from **12,637** examined record cards.
The presence of the intestinal helminthiasis was excluded by the coproparasitological test in all these patients in conformity with data from the record cards.

535 (40, 9%) patients had been present to additional serological investigations from 1308 invited persons.

– The positive results by the reveal of antibodies *vs* larva S_2 *Toxocara canis* IgG with the titer ≥11 were registered in 315 (58,9%) patients.
Most frequent they were constated in patients from the adult Allergology Unit (82,9%), Pneumophthisiology Unit (73%), and more rarely– in Children Allergology Unit (25%).
Parasitosis is a serious risk for children and adults who possess dogs and cats.
Larvae have a mecanic, traumatic, infectious, and toxicoallergic activity on tissues.

Thus, eosinophilia and tissue necrosis appear.

Eosinophils have a decisive importance in the formation of antiparasitar immunity. They, together with immunoglobulin E, basophil and

macrophage cells realise the organism protection. Reaction of immune complexes is resposable for the apparition of **fever**, **urticaria** and **generalised limphadenopathy**. Sensitized T lymphocites, collected around the larva, excrete lymphokines, attract macrophages and other cells, make them more active and a **granuloma** is modelled in this way. Granuloma may be produced in any organ or any tissue.

A necrosis zone is determined in the granuloma center by histological study, and eosinophils, histiocytes, neutrophils, lymphocytes, macrophages and epithelioid cellular conglomerates are determined to the periphery.

A particularity of this disease is the very various symptomatology, from asymptomatic forms (the most frequent) to extremely severe forms.

The invasion has manifestation by dyspeptic syndrome, hepatomegaly, transaminases high level in case of liver lesion.
The application of antilarvae drugs with various active substances, recommended in the treatment of this very frequent parasitosis, are **inefficient**.

More of it, they may produce one supplementary lesion of liver by the raise of hepatocytolitic syndrome.

► In this study we aimed to determine the clinical and laboratory efficacy of PRM medicines – **Interleukine 5** *low dose* in association with **Citomix** in patients with various manifestations of larval toxocarosis to whom previous standard conventional antihelmintic treatment courses were no effective, clinically and laboratory.

– The detection in these patients of cell immunodeficiency in various degrees with the lesion of balance between immunocompetent cells was an additional argues for the prescription of these PRM *low dose* medicines.

Published studies cannot demonstrate the role of the immunodeficiency, expressed by leucopenia and various degrees of the T-lymphocytes decrease, in the raise favourisation of antitoxocara antibodies titers or in the level decrease of them. The association of toxocarosis in immunocompromised patients has been not enough studied. Few researchers demonstrated, that *Toxocara* has a particular aspects in immunocompromised patients.

– Thus, we considered useful to clear up the toxocarosis particular aspects in patients, **who before did not respond previously to antitoxocara therapy**, with a long-acting evolution of the disease, which is linked to various immunodeficiencies.

– In the same aspect we tried to appreciate the effect of the complex *low dose low diluted* immunomodulator treatment on clinical and laboratory data.

MATERIALS AND RESEARCH METHODS

We have realized a clinical prospective and retrospective study, that involved **16 patients** suffering from various forms of larval toxocarosis, supervised in the Unit of Parasitology and Tropical Diseases of the Clinic of Contagious Diseases "Toma Ciorba" - Chişinău, Republic of Moldova.

Clinical and laboratory manifestations intensity in these patients a little or not at all given up to repeated courses of antilarva therapy by using some drugs, including those from the group derived from *bensimidasol*.
– Selection criteria were: long-acting presence of antitoxocara antibodies, presence of clinical and laboratory data eloquent for this disease, failure or partial efficiency of the antecedent therapeutic courses.

There were dynamic looked after most parameters to these patients:

- Clinical manifestations
- Biological manifestations (hemogram with the level of eosinophils, levels of immunoglobulin E, transaminases)
- Immunological parameters, (tests of II and III generation)
- Serological (viral hepatitis markers)
- Serical-parasitological tests (titer level of antitoxocara antibodies)
- Coproparasitological and seroparasitological tests for excluding other parasitic diseases, which may influence the level of antitoxocara antibodies.

RESULTS AND DISCUSSIONS

The patients group was homogenous from point of view of gender distribution: 50% men; 50% women.
All patients were symptomatic at the moment of the diagnosis, invoking different polyorganic lesions. This may be explained by the fact, that the reveal of toxocara infection is real after the ap-

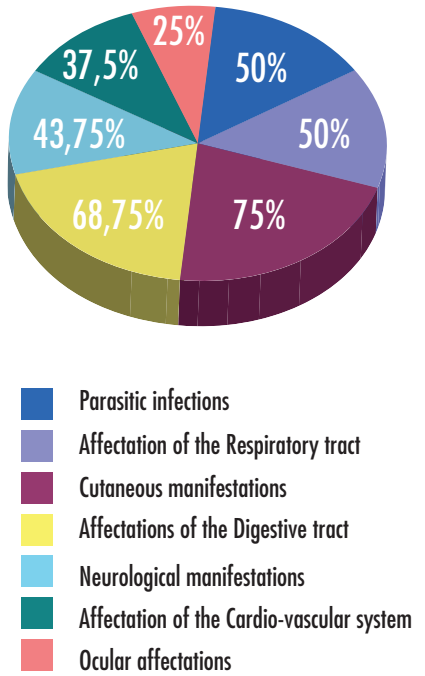


FIG. 1

Patients *ratio* in dependence of clinical aspects before treatment.

pearance of disturbance to the level of different organs and Systems.
The patients' *ratio* in dependence of the clinical aspects was: affectation of Respiratory tract: **8** (50%); dermatological manifestations: **12** (75%); affectations of the Digestive tract: **11** (68, 75%); neurological manifestations: **7** (43, 75%); affectation of Cardiovascular system: **6** (37, 5%); ocular affectations: **4** (25%) (FIG. 1).
– All patients had two or more clinical forms.

Two patients (12, 5%) had a chronic viral hepatitis C; one (6, 25%) had a chronic viral hepatitis B; one (6, 25%) had a mixed chronic viral hepatitis B+C; eight had parasitic infections.

All patients before treatment with **Citomix** and **Interleukin 5** *low dose* had a leucopenia, blood hipereosinophilia, and raised titers of antitoxocara antibodies.

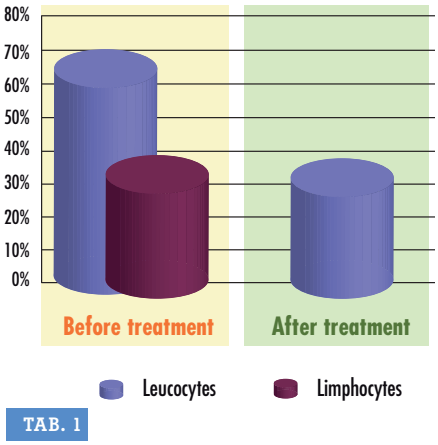
Immunodeficiency in different degree was diagnosed in more of half of the patients (58,0%).
Immunological tests in these patients demonstrated a raise of CIC in 25%, *ratio* lymph. T / lymph. B decreased in 9 patients (81,81%), *ratio* of immunoregulator index was decreased in 7 (63,63%).

Biological data in these patients demonstrated that only in 6 (37, 5%) from the 16 patients before the treatment with Citomix and IL-5 had not transaminase modifications, and in 10 (62, 5%) hepatocytolisis syndrome was present (moderate level raise– till 2 until 5 time in comparison with normal values).
Timol test was raised in 6 patients (37,5%), and in 10 (62,5%) was normal. The raised level of the timol test was accompanied by hyperalatemia in all cases.

Treatment with **INTERLEUKIN-5** *low dose* and **CITOMIX** (Guna Laboratories, Milan - I) was lasting 60 days and was in conformity with the protocol:

– **Citomix**, 10 granules sublingual in the morning and evening, one hour before meals for the first 5 days; next days, 3 granules.
– **Interleukin-5** *low dose*, 20 drops, 2 times a day sublingual, 20 minutes after Citomix administration.
On Sundays – pause.
The treatment was tolerated very well by all patients; side effects were no registered in any patient included in the study.

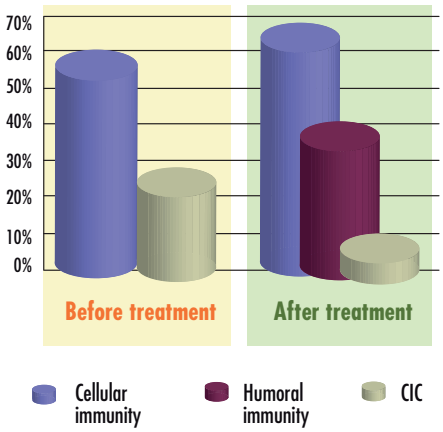
The clinical amelioration was established in the majority of the cases, the best positive effect was registered in patients with **dermatological manifestations** by the long-acting disappear of eruptive syndrome, cutaneous itching in 7 (58, 33%) from 12 patients with tegument syndrome of the disease.
In other 5 cases eruption and prurigo were less pronounced; 5 patients were requested a repeating treatment with Citomix and interleukin-5.
Ten (83, 33%) from these 12 patients were giveed up to regular using or antihistaminic medicines.
The strong amelioration of the general condition was accompanied by good paraclinical, biochemical, immunological and serological indices.
For example, leucocytes and lymphocytes indices in patients treated with Citomix + Interleukin-5 *low dose* were demonstrated the benefic influence of them. (TAB. 1)
Leucocytes formula was normal after treatment in **67%** of the patients and an unimportant leucopenia was registered in 33% patients only.



TAB. 1

This leucopenia has the tendency to rise, being to the lower normal values.
Lymphocytosis before the treatment was established in 34% patients, and after treatment the level of lymphocytes was normal in **100 %** patients.

The persistent T cell immunodeficiency was observed initially in 58% of cases, which were returned to normal levels after the treatment in 66% of initially revealed patients (58%), but in 34% of the cases the T cell immunity values were no suffered essentially modifications, consisting in 38,28% from persons initially revealed (TAB. 2).
There was established a rise of B lymphocytes up to normal values in 38% cases, that is conditioned by an effector antiparasitar immune response.

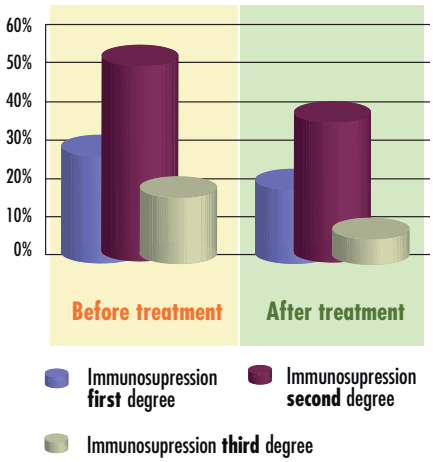


TAB. 2

CIC raised initially in 25% of the examined patients only; the raised values after the treatment persisted in one patient only (6, 25%).

There were established immunodeficiencies in different degrees before and after treatment (TAB. 3).
Before treatment: **first degree** of cellular immunodeficiency in **29%**; **second degree** in **53%**; **third degree** in **18%** of cases.

True ameliorations in all patients group were established after the treatment.
Only in 34% from initially revealed pa-



TAB. 3

tients (58%) was determined an amelioration with the tendency of passing from a more advanced immunodeficiency to another less important.

After treatment we obtained the following data: first degree in **20%** of the cases, second degree in **7%** of the cases, third degree in 6 % of the cases.

– The hepatic cytolysis syndrome diminished, coming back to normal values in 8 (80%) on 10 cases.
– The timol test decreased till normal values in 4 patients (66,6%).
– The serum values of eosinophils normalized in 43,8% of the cases, decreasing, actually, as a serum concentration of Ig E to the majority of patients.

Toxocara titers were decreased in **half of patients** too, but without the return to normal values in any patient from the study. It may be considered, in this case, possibly, as a serum sequela, which will persist and will need a long-lasting supervision, with one subsequent evaluation of total recovery.

CONCLUSIONS AND RECOMMENDATIONS

- Physiological regulating treatment with Interleukin-5 *low dose* and Citomix in patients with larval toxocarosis has been well tolerated without any negatve side effect during and after the treatment;
- The present study demonstrates the superior clinical therapeutic and laboratory efficacy of Citomix and Interleukin-5 *low dose* in patients with larval toxocarosis in comparison with previous therapeutic courses with drugs belonging to the group of *bensimidasol*, which are utilized in the intra- and extra intestinal nematodosis treatment, including toxocarosis;
- The treatment with Citomix and Interleukin-5 *low dose* may be recommended to patients suffering from larval toxocarosis, especially in forms with the long-lasting evolutions with failure in "classic" therapy, accompanied by different degrees of immunodeficiency;
- The efficacy of the association of Citomix + Interleukin-5 *low dose* may be advantageous and needs to be studied in the treatment of other invasions with chronic, long-lasting evolution, accompanied by invasive-allergic manifestation and different degrees of immunodeficiency.
- It is very interesting to study the therapeutic efficacy of these 2 PRM medicines with complex action in patients with chronic viral hepatitis in association with toxocarosis.
  This association is no rarely found in Republic of Moldova.
- This study needs to be continued by the extension and evaluation after a longer period of observation. ■

author's address

Prof. Gheorghe Plăcintă, M.D.
– Head physician of the Center of Clinical Parasitology.
Republican Hospital of Contagious Diseases "Toma Ciorba".
Chişinău - Republic of Moldova