doi: http://dx.doi.org/10.11606/issn.1679-9836.v102i5e-210459 Rev Med (São Paulo). 2023 Sept-Oct;102(5):e-210459

Article review

Pharmacological treatment of strongyloidiasis in humans: an integrative review

Tratamento farmacológico da estrongiloidíase em humanos: uma revisão integrativa

Jefferson Noronha Bezerra Silva[1], Marcilyo Max Bezerra Soares[2], Edvaldo Lucas da Costa da Silva[3], Daniel Matos de Sousa[4], Hérmeson Sttainer Silva Oliveira[5], Antonio Ferreira Mendes-Sousa[6]

Silva JNB, Soares MMB, Silva ELC, Sousa DM, Oliveira HSS, Mendes-Sousa AF. Pharmacological treatment of strongyloidiasis in humans: an integrative review / *Tratamento farmacológico da estrongiloidíase em humanos: uma revisão integrativa.* Rev Med (São Paulo). 2023 Sept-Oct;102(5):e-210459.

RESUMO: Introdução: A estrongiloidíase é uma parasitose endêmica no Brasil e em boa parte do mundo, causada pelo *Strongyloides stercoralis*, que se destaca por sua propriedade de causar autoinfecção no hospedeiro, podendo levar a quadros graves em situações de imunossupressão. Atualmente, a medicina dispõe de arsenal terapêutico limitado para esta infecção. **Objetivo**: Descrever as recomendações, novas possibilidades e a eficiência dos tratamentos farmacológicos mais atuais para estrongiloidíase. **Método**: Trata-se de uma revisão integrativa de literatura, utilizando as bases de dados PUBMED, Biblioteca Virtual de Saúde e SciELO, de publicações dos últimos 5 anos e com alto nível de evidência. **Resultados**: Após aplicação dos critérios de elegibilidade, 10 estudos foram selecionados para serem analisados de forma qualitativa. **Discussão**: O tratamento padrão para estrongiloidíase permanece sendo a ivermectina por via oral, reservando-se o albendazol e tiabendazol como terapia de segunda linha. O rastreio e tratamento da estrongiloidíase a todos os pacientes que necessitem de terapia imunossupressora é recomendado, incluindo corticoterapia para COVID-19 ou uso de metotrexato. Embora não seja recomendada para crianças com menos de 15 kg por falta de estudos de segurança, a ivermectina já foi utilizada neste público em certas situações, sem grandes efeitos adversos. Inclusive, sendo recomendada, de forma diluída, pela Agência Reguladora Francesa de Medicamentos, para crianças menores. A moxidectina está sendo estudada como uma possível alternativa à ivermectina principalmente por oferecer algumas vantagens farmacocinéticas. Na síndrome de hiperinfecção, uma formulação veterinária de ivermectina subcutânea tem sido utilizada em pacientes que não suportam a via oral. **Conclusão**: Discretos avanços foram realizados a respeito da terapia farmacológica para estrongiloidíase. Dentre as principais demandas, destaca-se a urgência de estudos clínicos que testem a ivermectina por via parenteral e sua segurança em crianças abaixo dos 15 kg.

DESCRITORES: Tratamento Farmacológico da COVID-19; Estrongiloidíase; Revisão.

ABSTRACT: Introduction: Strongyloidiasis is an endemic parasitosis in Brazil and in whole world, caused by *Strongyloides stercoralis*, which stands out for its ability to cause autoinfection in the host, which can lead to serious conditions in situations of immunosuppression. Currently, medicine has a limited therapeutic arsenal for this condition. **Objective**: To describe the recommendations, new possibilities and efficiency of the most current treatments for strongyloidiasis. **Method**: This is an integrative literature review, using the PUBMED, Virtual Health Library and SciELO databases, of publications from the last 5 years and with a high level of evidence. **Results**: After applying the eligibility criteria, 10 studies were selected to be analyzed qualitatively. **Discussion**: The standard treatment for strongyloidiasis remains oral ivermectin, reserving albendazole and thiabendazole as second-line therapy. Strongyloidiasis screening and treatment is recommended for all patients requiring immunosuppressive therapy, including corticosteroid therapy for COVID-19 or use of methotrexate. Although not recommended for children weighing less than 15 kg due to lack of safety studies, ivermectin has already been used in this population in certain situations, without major adverse effects. It is even recommended, in a diluted form, by the French Medicines Regulatory Agency, for younger children. Moxidectin is being studied as a possible alternative to ivermectin because it mainly offers some pharmacokinetic advantages. In hyperinfection syndrome, a veterinary formulation of subcutaneous ivermectin has been used in patients who cannot tolerate the oral route. **Conclusion**: Discreet advances have been made regarding pharmacological therapy for strongyloidiasis. Among the main demands, the urgency of clinical studies that test parenteral ivermectin and its safety in children below 15 kg stands out.

KEYWORDS: COVID-19 Drug Treatment; Strongyloidiasis; Review.

1. Universidade Federal do Piauí, Picos, (PI), Brasil. Acadêmico do curso de medicina. https://orcid.org/0000-0001-5648-2457. E-mail: jefin_nbs@hotmail.com
2. Universidade Federal do Piauí, Picos, (PI), Brasill. Acadêmico do curso de medicina. https://orcid.org/0000-0002-9385-7649. E-mail: marciliomaxxx@gmail.com
3. Universidade Federal do Piauí, Picos, (PI), Brasil. Acadêmico do curso de medicina. https://orcid.org/0000-0003-3966-9767. E-mail: dredvaldocosta@gmail.com
4. Universidade Federal do Piauí, Picos, (PI), Brasil. Acadêmico do curso de medicina. https://orcid.org/0000-0003-2089-1480. E-mail: Daniel.matos846@gmail.com
5. Universidade Federal do Piauí, Picos, (PI), Brasil. Acadêmico do curso de medicina. https://orcid.org/0000-0002-5522-2247. E-mail: hérmeson.oliveira@hotmail.com
6. Universidade Federal do Piauí, Picos, (PI), Brasil. Professor orientador do curso de medicina. Universidade Federal do Piauí, Picos, PI. https://orcid.org/0000-0002-2019-1348. E-mail: antoniofms@ufpi.edu.br

Endereço para correspondência: Jefferson Noronha Bezerra Silva. Rua Abdias Alves Araújo, 31, Bairro Horácio Alves, Parambu, Ceará, Brasil. E-mail: jefin_nbs@hotmail.com

INTRODUCTION

Strongyloidiasis is a parasitic disease caused by *Strongyloides stercoralis*, a helminth transmitted mainly through the soil, which infects more than 370 million people worldwide[1]. Its global prevalence is estimated at 8.1%[2] and up to 40% of the population is infected in some areas of the world[3]. The disease is endemic in Brazil and has a prevalence of approximately 20%[4].

In the life cycle of the parasite, filarial larvae in contaminated soil penetrate human skin, fall into the bloodstream and are taken to the lungs, where they penetrate the alveolar spaces. In the lungs, they are transported through the bronchial tree to the pharynx, are swallowed and reach the small intestine, where they become adult worms[5].

The female parasites are parthenogenetic and reproduce by laying eggs from which rhabditiform larvae hatch and are eliminated in the feces, or turn into filarioid larvae that can penetrate the intestinal mucosa and perpetuate the infection[6]. Autoinfection explains the existence of infection in people who have not been to endemic areas for many years[5].

Molting of rhabditiform larvae into filarioids is accelerated under immunosuppression, allowing massive numbers of larvae to self-infect the host and spread throughout the body. This process is called disseminated hyperinfection and has mortality rates of up to 70%[7].

The main trigger of this process is corticosteroid therapy, but transplanted patients, neoplastic patients or those under immunosuppressive therapy, are also at risk[8]. HTLV-1 infection is also a risk factor[9]. The hyperinfection syndrome was observed in the COVID-19 pandemic after starting corticosteroid therapy[10].

Low socioeconomic status is the main risk factor for strongyloidiasis; poor housing and sanitation, walking barefoot and living in places where open defecation occurs. There are other risk factors for hyperinfection, such as rheumatic diseases, asthma and glomerulonephritis, mainly related to the use of corticosteroids and immunosuppressive medications in these pathologies. There are also some minor factors, such as malnutrition, end-stage renal disease, diabetes mellitus, diverticulosis and blind bowel loops[5].

In the acute phase, strongyloidiasis may present rash due to intradermal migration of larvae, itching, epigastric tenderness, diarrhea, nausea/vomiting, low-grade fever and eosinophilia. As a result of the pulmonary cycle, the so-called Loeffler Syndrome may appear, characterized by wheezing, coughing, and migratory interstitial infiltrates. In the chronic phase, perianal rash, vague abdominal complaints, intermittent diarrhea (alternating with constipation), occasional nausea and vomiting, weight loss, itching or chronic urticaria may appear[5].

In hyperinfection due to disseminated strongyloidiasis, the following findings stand out: abdominal pain, intestinal obstruction, mucosal ulceration and peritonitis, intestinal hemorrhage, dyspnea, pneumonia, hemoptysis, meningitis, pancreatitis, cholecystitis, liver abscess, gram-negative sepsis resulting from the larvae that transport bacteria through the mucosal walls, among others[11].

However, most infected people are asymptomatic or have mild and nonspecific complaints[12]. In addition, commonly used diagnostic methods lack sensitivity[5], and serological tests are the most sensitive diagnostic tools available nowadays[13]. Although the definitive diagnosis is made by identifying the larvae in the stool, in hyperinfection, larvae can be found in respiratory secretions, cerebrospinal fluid, peritoneal fluid, blood and other samples[6].

Regarding diagnosis, stool analysis with Baermann techniques and agar culture are the best fecal methods currently[5]. However, a post-treatment evaluation with parasitological methods does not reliably exclude infection, as the sensitivity of these methods is low[14]. Although the direct observation of a single stool sample is not very sensitive, the sensitivity of the test increases to 50% with three samples and may reach near 100% with seven stool samples in a row[15].

Polymerase Chain Reaction (PCR) tests to detect *Strongyloides* in stool samples have already been developed[4] and can reach sensitivity of 61.8% and specificity of 95%[16]. However, PCR tests are not widely available.

Although no global public health strategy against the disease has been created to date, the anthelmintic ivermectin was placed on the list of essential medicines by the World Health Organization (WHO) in 2017[5]. Ivermectin is a macrocyclic lactone and acts on chloride channels controlled by helminth glutamate, leading to paralysis and death[17]. Given its lesser efficacy, benzimidazole constitutes the second-line therapy for strongyloidiasis[18].

However, ivermectin is not recommended for children weighing less than 15 kg since evidence of safety is lacking. For this reason, other less effective or more toxic alternatives are used. Although there is this contraindication for ivermectin, it is likely that thousands of young children have already received ivermectin during campaigns in Africa[19].

In humans, ivermectin is currently available for oral administration (PO) only, making it difficult to treat patients who do not support this route. In addition, there is the prospect of drug resistance given its mass administration, both in the pandemic, as an attempt at treatment for COVID-19, and in control programs for onchocerciasis and filariasis[17].

Thus, considering the worldwide relevance that strongyloidiasis still represents and the scarcity of therapeutic possibilities, the aim of this work was to carry out a scientific literature review in order to know and describe the recommendations, new possibilities and efficiency of the most current treatments for strongyloidiasis.

METHOD

This is an integrative literature review in which the subsequent stages were followed: 1) Determine the research question; 2) Investigation of the scientific literature; 3) Sorting of results; 4) Choice and evaluation of studies; 5) Interpretation, analysis, and discussion of findings; 6) Production of the review in text format[20,21].

This study was focused on the following question: What is the most current and important scientific literature about the pharmacological treatment of strongyloidiasis in humans?

Scientific evidence can be classified hierarchically depending on the methodology used in each study. To help choose the best possible evidence, this study was based on the hierarchy of evidence proposed by Melnyk[22]. Studies are subdivided into seven levels, of which only levels 1 (systematic reviews, meta-analyses and clinical guidelines) and 2 (randomized clinical trials - RCTs) were elected to enter the sample.

The literature search was carried out in the following databases: SciELO, PubMed/Medline and Virtual Health Library (VHL). The search terms used were in accordance with the Health Sciences Descriptors (DeCS/MeSH) and combined as follows: (Estrongiloidíase OR Strongyloidiasis OR Estrongiloidiasis) AND ("tratamento farmacológico" OR "drug therapy" OR "tratamiento farmacológico").

The following inclusion criteria were used in the search: full-text access; publications within a maximum period of up to five years from the search date; and human studies. No language restrictions were applied.

Searches in databases were carried out in December 2022. The following exclusion criteria were established to refine the sample: repeatedly indexed articles; articles that did not meet the objectives of this review after reading the titles and abstracts; and articles with imprecise methodology.

RESULTS

Initially, 2,657 articles were found. After disregarding duplicate articles and applying the inclusion criteria, 27 articles remained. After reading the titles, abstracts and methodologies of the works, ten articles remained. Their full texts were read and analyzed; six of these articles were from PubMed and four from VHL. The SciELO database did not show results for the search. The flowchart (Figure 1) illustrates in a didactic way how the article selection process was performed.

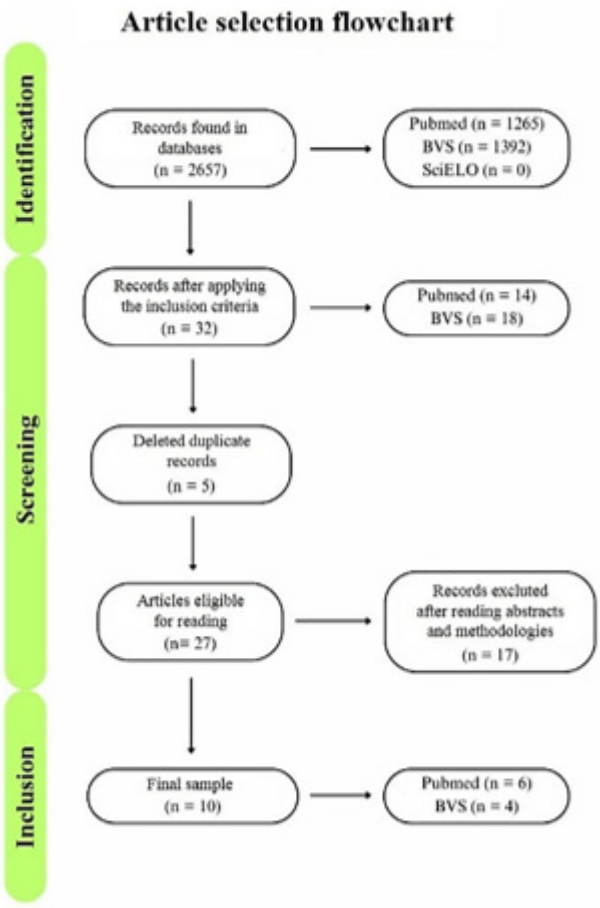

Figure 1 - Article selection flowchart.

Two data collection instruments were used to assist in the research, represented respectively in Table 1 and Table 2. In Table 1, we sought to identify the studies, highlighting the title, main author, year and journal. In Table 2, the characterization of studies was performed based on a qualitative analysis from the reference, methodology, level of evidence and results of interest of each article.

Table 1 - Identification of studies used.

Title	Main author	Year	Journal
Clinical and laboratory features of *Strongyloides stercoralis* infection at diagnosis and after treatment: a systematic review and meta-analysis.	Buonfrate D, et al.	2021	Clinical Microbiology and Infection.
Comparison of Trials Using Ivermectin for COVID-19 Between Regions With High and Low Prevalence of Strongyloidiasis: A Meta-analysis.	Bitterman A, et al.	2022	JAMA Network open.
Multiple-dose versus single-dose ivermectin for *Strongyloides stercoralis* infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial.	Buonfrate D, et al.	2019	The Lancet Infectious Diseases.
Efficacy and safety of ascending doses of moxidectin against Strongyloides stercoralis infections in adults: a randomised, parallel-group, single-blinded, placebo-controlled, dose-ranging, phase 2a trial.	Hofmann D, et al.	2021	The Lancet Infectious Diseases.
Methotrexate exposure and risk of strongyloidiasis.	Richards C, et al.	2019	Tropical Medicine & International health.
A systematic review and an individual patient data meta-analysis of ivermectin use in children weighing less than fifteen kilograms: Is it time to reconsider the current contraindication?	Jittamala P, et al.	2021	PLOS Neglected Tropical Diseases.
Optimizing moxidectin dosing for *Strongyloides stercoralis* infections: Insights from pharmacometric modeling.	Hofmann D, et al.	2022	Clinical and Translational Science.
World Gastroenterology Organisation Global Guidelines: Management of Strongyloidiasis February 2018 - Compact Version.	Farthing, M, et al.	2020	Journal of Clinical Gastroenterology.
Evidence-Based Guidelines for Screening and Management of Strongyloidiasis in Non-Endemic Countries.	Requena-Méndez A, et al.	2017	The American Journal of Tropical Medicine and Hygiene.
Intestinal parasites including *Cryptosporidium, Cyclospora, Giardia*, and *Microsporidia, Entamoeba histolytica, Strongyloides, Schistosomiasis*, and *Echinococcus*: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice.	La Hoz RM, et al.	2019	Clinical Transplantation

Table 2 - Characterization of studies used.

Reference	Methodology	Main results
BUONFRATE et al.[23]	Systematic review with meta-analysis of nine RCTs and 13 prospective observational studies. Level 1 of evidence.	Ivermectin (200 µg/kg PO single dose) was superior to albendazole (400 mg/day PO for three days), although not 100% effective in larval elimination.
BITTERMAN et al.[24]	Systematic review with meta-analysis of RCTs taken from the c19ivermetin database. Level 1 of evidence.	Twelve studies totaling 3,901 patients showed that when COVID-19 patients from areas with a high prevalence of strongyloidiasis underwent treatment with ivermectin, they had lower mortality.
BUONFRATE et al.[25]	Controlled, multicenter, open-label, phase three RCT of 231 patients analyzed after 12 months. Study in non-endemic countries to exclude reinfection. Level 2 of evidence.	Multiple doses were not superior to a single dose of ivermectin in the treatment of strongyloidiasis, suggesting that the co-administration of ivermectin and albendazole in a single dose would increase the effectiveness of control programs in endemic communities.
HOFMANN et al.[26]	Phase 2A, parallel-group, double-blind, placebo-controlled, dose-ranging RCT of 209 adults in the final sample. Level 2 of evidence.	Moxidectin is easily administered as a single dose regardless of weight and is effective against ivermectin-resistant strains. A dose of 8 mg is recommended.
RICHARDS et al.[27]	Systematic review of the literature on 27 studies reporting 29 cases of humans exposed to methotrexate and tested for *Strongyloides*. Level 1 of evidence.	Screening and treatment of strongyloidiasis should be considered for patients using methotrexate, as 52% of people experienced hyperinfection, even when using low doses.

continue

continuation

Reference	Methodology	Main results
JITTAMALA et al.[19]	Systematic review with meta-analysis of 17 reports with 1,088 children under 15 kg who used ivermectin. Level 1 of evidence.	Data indicate that ivermectin can be used for children below 15 kg, as adverse effects occurred in only 1.4% of children, all of which were mild and self-limiting, even with more than one dose.
HOFMANN et al.[28]	Phase 2A, parallel-group, double-blind, placebo-controlled, dose-ranging RCT with 209 adults in the final sample. Level 2 of evidence.	180 out of the 209 patients with strongyloidiasis in the study received moxidectin 2 to 12 mg with cure rates of 73% to 97%. The remaining patients received placebo, showing a 14% cure rate. There were no large gains with the mean cure rate at the 8 mg dose (88% cure) versus the 12 mg dose (90% cure). Cure rates are dependent on the intensity of the infection (number of larvae per gram of feces); 97% with 8 mg in low-intensity infections, and 90% in moderate and high-intensity infections.
FARTHING et al.[5]	Clinical practice guideline. Level 1 of evidence.	Healing control should be done through a drop in serological titers and a negative fecal exam. If there is therapeutic failure, ivermectin can be repeated for two days. It is recommended to look for strongyloidiasis in patients with eosinophilia. The safety of ivermectin in pregnancy has not been established. Use it only if at risk of hyperinfection. Breastfeeding women should only be treated with ivermectin if the benefits outweigh the risks of excretion in milk for the newborn. Ivermectin can be used subcutaneously when the oral route is unavailable.
REQUENA-MÉNDEZ et al.[14]	Clinical practice guideline. Level 1 of evidence.	If an appropriate diagnostic test is not available, ivermectin treatment should be provided preventively. RCTs showed that high-dose albendazole (800 mg/day for three days) and thiabendazole (1 g every 12 hours for five days) showed high cure rates, although with greater adverse effects, particularly thiabendazole.
LA HOZ et al.[6]	Clinical practice guideline. Level 1 of evidence.	Transplant candidates or transplant recipients with strongyloidiasis should be screened for HTLV-1, as co-infection is associated with post-treatment relapse. Subcutaneous or rectal ivermectin can be used in hyperinfection in patients who cannot tolerate PO.

DISCUSSION

The morbidity and mortality of strongyloidiasis is mainly linked to hyperinfection in immunocompromised individuals. However, the disease can present several uncomfortable symptoms in immunocompetent people. Therefore, the screening and treatment of risk groups is important, even in non-endemic areas, as well as the intensification of control actions in endemic countries such as Brazil, both for symptom relief and prevention of the disseminated disease[23].

Considering the risk of hyperinfection, all patients with strongyloidiasis should be treated, as spontaneous cure cannot be expected because of autoinfection[5]. In addition, screening should be mandatory in immunosuppressed patients[14]. The reliable diagnosis of patients at risk is necessary for treatment before starting immunosuppression or in patients infected with HTLV-1 or HIV[5].

In resource-limited endemic areas, a plausible approach would be to treat all transplant candidates. In endemic areas with available diagnostic tools, a universal screening approach can be used. In non-endemic areas, screening should be guided by risk factors for strongyloidiasis[6], which include people who were born, have lived or traveled to endemic tropical or subtropical regions and with unexplained eosinophilia[14].

As corticosteroid therapy is the main trigger for hyperinfection, empirical treatment of patients at risk for strongyloidiasis with ivermectin is prudent before initiating corticosteroid therapy for COVID-19[24]. Furthermore, if emergency immunosuppression is required and diagnostic tests are not readily available, empiric therapy with ivermectin should be considered[5].

The same reasoning can be applied to patients who will start therapy with methotrexate, used in several rheumatological and dermatological diseases, as it is associated with a greater risk of hyperinfection given its immunosuppressive effects, even at low doses. In the absence of contraindications (pregnancy or lactation), it is reasonable to consider prophylactic treatment with ivermectin if screening is not feasible[27].

In addition, it has already been demonstrated that ivermectin is highly effective even in a single dose, which facilitates the treatment of patients and allows its simultaneous use with albendazole, also in a single dose, in parasite control programs in communities, increasing coverage for *Strongyloides*[25]. The current recommendation for ivermectin is 200 µg/kg in a single dose, although some experts suggest that multiple doses increase efficacy, and the WHO itself offers both options: single dose; or two doses on consecutive days[14].

Although a consistent decrease in the prevalence of *Strongyloides* has been demonstrated after filariasis

and onchocerciasis elimination programs with the use of ivermectin, preventive treatment for strongyloidiasis is still not recommended by the WHO nor included in the control strategy for soil-transmitted helminths[5].

This corroborates the review by Jittamala[19], which states that the use of ivermectin for children weighing less than 15 kg can benefit the health of this group, as administration of ivermectin in control programs in Colombia, Ecuador, Argentina and Australia demonstrated reductions in the prevalence of strongyloidiasis.

However, ivermectin comes in 3 mg or 6 mg tablets and can be difficult for children to swallow. As no pediatric formulation is available in France, the French Medicines Regulatory Agency recommends crushing a whole 3 mg tablet for children weighing 10-15 kg, or half a tablet for children weighing less than 10 kg, and mixing in 10 mL of water for oral administration[29].

In Latin America, an oral liquid formulation for strongyloidiasis has been used in several trials for the treatment of young children in Colombia and Peru, and infants weighing less than 15 kg in Venezuela[19]. A randomized, double-blind, placebo-controlled, dose-escalation study called Ivermectin Safety in Small Children is currently ongoing and designed to evaluate the safety, pharmacokinetics, and efficacy of oral ivermectin in children infected with scabies weighing less than 15 kg[30].

Aiming at therapeutic alternatives for strongyloidiasis, a clinical trial has shown that moxidectin, a drug used in veterinary medicine, which has been approved for humans in the treatment of onchocerciasis, can help. Moxidectin is also a macrocyclic lactone and offers advantages over ivermectin: single oral dose independent of weight; lower neurotoxic potential; longer half-life with the potential to fight self-infection or reinfection; and effectiveness in the treatment of ivermectin-resistant *Strongyloides*[26].

According to Hofmann[28], a dose of 8 mg moxidectin was enough to saturate the glutamate-controlled chloride channels of the parasite, leading to its paralysis and elimination, which is the dose already approved for onchocerciasis. However, in highly infected individuals, cure cannot be expected with a single dose, as moxidectin, like ivermectin, acts only on adult worms[28]. This implies a possible relapse by migrating larvae or hatching eggs. Therefore, the extension of treatment period and multiple dosages can guarantee better results. Larger studies need to be conducted to better evaluate the effectiveness of moxidectin in humans.

One guideline also mentions an alternative therapeutic possibility to ivermectin, which would be high-dose albendazole (800 mg/day for five consecutive days), showing a cure rate of 95%, and thiabendazole (1g twice a day for five days) with a cure rate of 100%[14]. However, this approach has only been tested in a small number of patients (35) during a short follow-up period (three weeks).

There is also a paucity of data to determine the optimal treatment of *Strongyloides* hyperinfection syndrome, but management involves a combination of broad-spectrum antimicrobials for gram-negative bacterial sepsis, anthelmintic treatment, supportive care, and reduced immunosuppression, if possible[6].

With this in mind, ivermectin can be administered daily for a period of 14 days in critically ill people, and until body fluid tests for larvae become negative[5]. Ivermectin (200 µg/kg PO) can be used daily up to two weeks after the last positive stool sample to cover a complete cycle of autoinfection[6]. Some specialists still advocate a combination therapy with albendazole[31].

The global guideline[5] also states that in people with hyperinfection who are unable to take oral medications, ivermectin has been successfully used subcutaneously (application of two doses of 0.6 ml of a veterinary formulation of 10 mg/ml) according to the report by Chiodini[32].

In another guideline[6], the ideal treatment of critically ill patients unable to tolerate oral therapy is still uncertain, but options in this scenario include rectal[33] or subcutaneous[34] ivermectin at a dose of 200 mg/kg/day. Case reports have described subtherapeutic levels of rectal ivermectin[35], hence the recommendation to use the subcutaneous route[36]. From this, the use of the subcutaneous formulation of ivermectin for treatment in humans could obtain emergency approval from regulatory agencies as an experimental drug.

CONCLUSION

It is evident that strongyloidiasis still remains a serious public health problem worldwide, mainly because of hyperinfection in situations of immunosuppression. These situations tend to increase because of advances in transplant medicine and the increasing routine use of immunomodulators in clinical practice.

With this in mind, discrete advances have been made regarding pharmacological therapy for strongyloidiasis. Among the main demands, the urgency of clinical studies testing parenteral ivermectin and its safety in children below 15 kg stands out. In addition, global actions to combat this disease should be developed, especially in endemic countries, for greater control of this parasite and promotion of the population's health.

REFERENCES

1. Bisoffi Z, Buonfrate D, Montresor A, Requena-Méndez A, Muñoz J, et al. Strongyloides stercoralis: a plea for action. PLoS Negl Trop Dis. 2013;7(5):e2214. doi: 10.1371/journal.pntd.0002214.

2. Buonfrate D, Bisanzio D, Giorli G, Odermatt P, Fürst T, et al.

The global prevalence of strongyloides stercoralis infection. Pathogens. 2020;9(6):468. doi: 10.3390/pathogens9060468.

3. Schär F, Trostdorf U, Giardina F, Khieu V, Muth S, et al. Strongyloides stercoralis: global distribution and risk factors. PLoS Negl Trop Dis. 2013;7(7):e2288. doi: 10.1371/journal.pntd.0002288.
4. Buonfrate D, Mena MA, Angheben A, Requena-Mendez A, Muñoz J, et al. COHEMI Project Study Group. prevalence of strongyloidiasis in Latin America: a systematic review of the literature. Epidemiol Infect. 2015;143(3):452-60. doi: 10.1017/S0950268814001563.
5. Farthing M, Albonico M, Bisoffi Z, Bundy D, Buonfrate D, et al. World gastroenterology organisation global guidelines: management of strongyloidiasis February 2018-compact version. J Clin Gastroenterol. 2020;54(9):747-57. doi: 10.1097/MCG.0000000000001369.
6. La Hoz RM, Morris MI; AST Infectious diseases community of practice. intestinal parasites including cryptosporidium, cyclospora, giardia, and microsporidia, entamoeba histolytica, strongyloides, schistosomiasis, and echinococcus: guidelines from the american society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13618. doi: 10.1111/ctr.13618.
7. Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, et al. Severe strongyloidiasis: a systematic review of case reports. BMC Infect Dis. 2013;13:78. doi: 10.1186/1471-2334-13-78.
8. Keiser PB, Nutman TB. Strongyloides stercoralis in the Immunocompromised Population. Clin Microbiol Rev. 2004;17(1):208-17. doi: 10.1128/CMR.17.1.208-217.2004.
9. Siegel MO, Simon GL. Is human immunodeficiency virus infection a risk factor for Strongyloides stercoralis hyperinfection and dissemination. PLoS Negl Trop Dis. 2012;6(7):e1581. doi: 10.1371/journal.pntd.0001581.
10. Lier AJ, Tuan JJ, Davis MW, Paulson N, McManus D, et al. Case Report: disseminated strongyloidiasis in a patient with COVID-19. Am J Trop Med Hyg. 2020 Oct;103(4):1590-1592. doi: 10.4269/ajtmh.20-0699.
11. Centers for disease control and prevention. Parasites-strongyloides. Resources for health professionals. Atlanta, GA: Centers for disease control and prevention; 2016. Available from: www.cdc.gov/parasites/strongyloides/health_professionals/index.html.
12. González A, Gallo M, Valls ME, Muñoz J, Puyol L, et al. Clinical and epidemiological features of 33 imported Strongyloides stercoralis infections. Trans R Soc Trop Med Hyg. 2010;104(9):613-6. doi: 10.1016/j.trstmh.2010.06.001.
13. Buonfrate D, Formenti F, Perandin F, Bisoffi Z. Novel approaches to the diagnosis of Strongyloides stercoralis infection. Clin Microbiol Infect. 2015;21(6):543-52. doi: 10.1016/j.cmi.2015.04.001.
14. Requena-Méndez A, Buonfrate D, Gomez-Junyent J, Zammarchi L, Bisoffi Z, et al. Evidence-Based Guidelines for screening and management of strongyloidiasis in non-endemic countries. Am J Trop Med Hyg. 2017;97(3):645-652. doi: 10.4269/ajtmh.16-0923.
15. Nielsen PB, Mojon M. Improved diagnosis of strongyloides stercoralis by seven consecutive stool specimens. Zentralbl Bakteriol Mikrobiol Hyg A. 1987;263(4):616-8. doi: 10.1016/s0176-6724(87)80207-9.
16. Buonfrate D, Requena-Mendez A, Angheben A, Cinquini M, Cruciani M, et al. Accuracy of molecular biology techniques for the diagnosis of Strongyloides stercoralis infection-A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(2):e0006229. doi: 10.1371/journal.pntd.0006229.
17. Laing R, Gillan V, Devaney E. Ivermectin - Old Drug, new tricks? Trends Parasitol. 2017;33(6):463-72. doi: 10.1016/j.pt.2017.02.004.
18. Henriquez-Camacho C, Gotuzzo E, Echevarria J, White Junior AC, Terashima A, et al. Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection. Cochrane Database Syst Rev. 2016;16(1):CD007745. doi: 10.1002/14651858.CD007745.pub3.
19. Jittamala P, Monteiro W, Smit MR, Pedrique B, Specht S, et al. A systematic review and an individual patient data meta-analysis of ivermectin use in children weighing less than fifteen kilograms: Is it time to reconsider the current contraindication? PLoS Negl Trop Dis. 2021;15(3):e0009144. doi: 10.1371/journal.pntd.0009144.
20. Mendes KDS, Silveira RCCP, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. Texto Contexto – Enferm Florianópolis. 2008;17(4):758-64. doi.org/10.1590/S0104-07072008000400018.
21. Souza MT, Silva MD, Carvalho R. Integrative review: what is it? How to do it?. Einstein (São Paulo). 2010;8(1):102-6. doi.org/10.1590/S1679-45082010RW1134.
22. Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare. A guide to best practice. Philadelphia: Lippincot Williams & Wilkins; 2005.
23. Buonfrate D, Fittipaldo A, Vlieghe E, Bottieau E. Clinical and laboratory features of Strongyloides stercoralis infection at diagnosis and after treatment: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(11):1621-8. doi: 10.1016/j.cmi.2021.07.016.
24. Bitterman A, Martins CP, Cices A, Nadendla MP. Comparison of trials using Ivermectin for COVID-19 Between regions with high and low prevalence of Strongyloidiasis: a meta-analysis. JAMA Netw Open. 2022;5(3):e223079. doi: 10.1001/jamanetworkopen.2022.3079.
25. Buonfrate D, Salas-Coronas J, Muñoz J, Maruri BT, Rodari P, et al. Multiple-dose versus single-dose ivermectin for Strongyloides stercoralis infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. Lancet Infect Dis. 2019;19(11):1181-90. doi: 10.1016/S1473-3099(19)30289-0.
26. Hofmann D, Sayasone S, Sengngam K, Chongvilay B, Hattendorf J, et al. Efficacy and safety of ascending doses of moxidectin against Strongyloides stercoralis infections in adults: a randomised, parallel-group, single-blinded, placebo-controlled, dose-ranging, phase 2a trial. Lancet Infect Dis. 2021;21(8):1151-60. doi: 10.1016/S1473-3099(20)30691-5.

27. Richards C, Penner J, Colmegna I, Loewen H, Melaku Z, et al. Methotrexate exposure and risk of strongyloidiasis. Trop Med Int Health. 2019;24(9):1032-41. doi: 10.1111/tmi.13288.

28. Hofmann D, Smit C, Sayasone S, Pfister M, Keiser J. Optimizing moxidectin dosing for Strongyloides stercoralis infections: insights from pharmacometric modeling. Clin Transl Sci. 2022;15(3):700-8. doi: 10.1111/cts.13189.

29. Berthe-Aucejo A, Prot-Labarthe S, Pull L, Lorrot M, Touratier S, et al. Traitement de la gale et rupture d'Ascabiol(®) : quid de la population pédiatrique ? Gale chez l'enfant et rupture d'Ascabiol(®) [Treatment of scabies and Ascabiol(®) supply disruption: what about the pediatric population?]. Arch Pediatr. 2014;21(6):670-5. French. doi: 10.1016/j.arcped.2014.03.001.

30. Kobylinski K, von Seidlein L. Ivermectin safetyin small children (NCT04332068). University of Oxford; 2020.

31. Greaves D, Coggle S, Pollard C, Aliyu SH, Moore EM. Strongyloides stercoralis infection. BMJ. 2013 Jul 30;347:f4610. doi: 10.1136/bmj.f4610.

32. Chiodini PL, Reid AJ, Wiselka MJ, Firmin R, Foweraker J. Parenteral ivermectin in Strongyloides hyperinfection. Lancet. 2000;355(9197):43-4. doi: 10.1016/s0140-6736(99)02744-0.

33. Tarr PE, Miele PS, Peregoy KS, Smith MA, Neva FA, et al. Case report: rectal adminstration of ivermectin to a patient with Strongyloides hyperinfection syndrome. Am J Trop Med Hyg. 2003;68(4):453-5. PMID: 12875295.

34. Barrett J, Broderick C, Soulsby H, Wade P, Newsholme W. Subcutaneous ivermectin use in the treatment of severe Strongyloides stercoralis infection: two case reports and a discussion of the literature. J Antimicrob Chemother. 2016;71(1):220-5. doi: 10.1093/jac/dkv315.

35. Bogoch II, Khan K, Abrams H, Nott C, Leung E, et al. Failure of ivermectin per rectum to achieve clinically meaningful serum levels in two cases of Strongyloides hyperinfection. Am J Trop Med Hyg. 2015;93(1):94-6. doi: 10.4269/ajtmh.15-0077.

36. Grein JD, Mathisen GE, Donovan S, Fleckenstein L. Serum ivermectin levels after enteral and subcutaneous administration for Strongyloides hyperinfection: a case report. Scand J Infect Dis. 2010;42(3):234-6. doi: 10.3109/00365540903443165.

Received: 2023, April 10
Accepted: 2023, June 16