v. 4, n. 12, 2024

International Journal of Health Science

RECENT PHARMACOLOGICAL ADVANCES IN THE TREATMENT OF TUBERCULOSIS: AN UPDATED NARRATIVE BIBLIOGRAPHICAL REVIEW

Camila Agostinis Silva
Medicine course at: Universidade de São Paulo (FMUSP)
São Paulo - SP
https://orcid.org/0009-0005-0584-9702

Gabriella Montandon Lassi Nunes
Faculdade Ceres (Faceres)
São José do Rio Preto - SP
https://orcid.org/0009-0009-5625-4871

Erica Prevital Nery
Universidade para o Desenvolvimento do Estado e da Região do Pantanal (UNIDERP)
Campo Grande - MS
https://orcid.org/0009-0000-7576-5938

Maria Gabriela Franco Pereira
Universidad Internacional Três Fronteiras (UNINTER)
Pedro Juan Caballero - Paraguai
https://orcid.org/0009-0000-9508-2528

Hannah De Araújo Costa Dias
Faculdade Multivix (MULTIVIX)
Cachoeiro de Itapemirim - ES
https://orcid.org/0009-0009-9438-5856

Isadora Brunialti Morosi
Universidade Anhembi Morumbi (UAM)
Piracicaba - SP
https://orcid.org/0009-0004-5905-1360

Izadora Rosa Reinoso
Universidade para o Desenvolvimento do Estado e da Região do Pantanal (UNIDERP)
Campo Grande - MS
https://orcid.org/0009-0007-8016-1304

Maria Soledad Gaona Mendez
Universidad Nacional de Rosario (UNR)
Rosario - Argentina
https://orcid.org/0009-0002-9050-2073

Ana Carla Maia Rodrigues de Paula
Universidade Nilton Lins (UNINILTONLINS)
Manaus - AM
https://orcid.org/0009-0004-4041-7748

Manuela Moreira Galante
Universidade Nova Iguaçu - Campos X (UNIG)
Itaperuna - RJ
https://orcid.org/0009-0003-1957-356

Sara Silveira Lopes Ribeiro Benjamin
Centro Universitário Municipal de Franca (Uni-FACEF)
Franca - SP
https://orcid.org/0009-0000-0702-058X

Amanda Carolina Zicatti da Silveira
Pontifícia Universidade Católica de São Paulo
São Paulo - SP
https://orcid.org/0000-0001-8963-9553

Abstract: Goal: To evaluate recent pharmacological advances in the treatment of tuberculosis, focusing on their efficacy, safety and potential impact on clinical practice.
Methods: This is a Narrative Bibliographic Review carried out using the PubMed database platform. The search was constructed using the descriptors "tuberculosis", "management", "treatment strategy" and "new drugs", in association with the Boolean operators "AND" and "OR" and "NOT", resulting in 2126 initial articles. Due to the inclusion and exclusion criteria, only 26 became official sources. Discussion: The treatment of multidrug-resistant tuberculosis benefits from medications such as Bedaquiline, which offer efficacy and a reduction in treatment time. However, these medications raise concerns due to side effects significant side effects such as changes in the electrocardiogram and cardiotoxicity. The BPAZ regimen has been observed to react variously to changes in exposure to pyrazinamide and Bedaquiline. Additionally, the development of innovative technologies such as vaccines to prevent TB reinfection and immunotherapies to strengthen the immune response against latent tuberculosis is in focus, aiming to shorten the duration of the disease and prevent bacterial resistance. Final Considerations: The need to develop more effective and safe therapeutic options for the treatment of tuberculosis and its resistance is evident. Understanding both the benefits and adverse effects of current drugs is crucial. Furthermore, vaccines and emerging immunotherapies promise to strengthen the immune system, prevent reinfections and combat resistance to tuberculosis, representing significant interventions in the fight against the disease.
Keywords: Tuberculosis, Treatment, New Drugs.

INTRODUCTION

Tuberculosis, an infectious disease caused by the bacterium Mycobacterium tuberculosis (Koch's Bacillus), remains an imminent challenge in global public health. Notably, the growing bacterial resistance to the treatment of this pathology has raised concerns, highlighting the need for effective and safe pharmacological advances, as well as their impact on clinical practice. Drug-resistant tuberculosis (DR-TB) intensifies the global burden of antimicrobial resistance, demanding a substantial share of healthcare budgets and related resources in numerous endemic countries. Recently, it was estimated that there were 465,000 incident cases of multidrug resistance/rifampin resistance (MDR/RR-TB) globally.

Furthermore, around 3.6% of new TB cases and 18% of previously treated TB cases progressed to MDR-TB in 2021 (DIRIBA G. et al., 2023).

Current standard anti-TB therapy (ATT), which involves daily administration of ethambutol, isoniazid, pyrazinamide and rifampicin for the first two months, followed by daily use of isoniazid and rifampin for the subsequent four months, has shown efficacy in more than 92 % of cases in clinical trials, achieving a treatment success rate of 85%. However, recurrence after successful treatment, ranging from 3.3–34.0% of cases, results in high drug resistance and mortality. Independent risk factors for TB recurrence include male sex, advanced age and comorbidities such as diabetes mellitus or chronic obstructive pulmonary disease (LEE C. et al., 2023).

The rapid emergence of resistance to new therapies against tuberculosis reiterates the importance of adequate antibiotic management and the development of new therapeutic regimens effective against drug-resistant strains in circulation (LIEBENBERG D. et al., 2022). Furthermore, migration, poor housing conditions, poverty, and the prevalence of other pathologies such as HIV and diabetes exacerbate the problem, making evidence-based diagnosis and treatment imperative. Furthermore, as highlighted by Dartois V.A. and Rubin V.J. (2022), despite two decades of intensive research with the aim of understanding and eradicating tuberculosis, biological uncertainties persist that impede progress. However, thanks to collaborative initiatives involving academia, the pharmaceutical industry, and nonprofit organizations, there is a promising set of drug candidates emerging. Pending formal validation, the challenge that remains is the global implementation of new flexible therapeutic guidelines, considering the inequalities in disease burden and the unique treatment challenges in different regions and subcontinents.

This article, through a literary review, aims to evaluate recent pharmacological advances in the treatment of tuberculosis. The focus is on the effectiveness, safety and potential impact of these advances on clinical practice, seeking to contribute to a more in-depth and updated understanding of this scenario, aiming to support more effective intervention strategies.

METHODOLOGY

This is a narrative bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "How effective and safe are recent pharmacological advances in the treatment of tuberculosis in patients diagnosed with the disease, and what is their potential impact on clinical practice?".

In this sense, according to the parameters mentioned above, the population or

problem of this research refers to patients with tuberculosis who are undergoing pharmacological treatment with new drugs or combinations of drugs that have recently been introduced for the treatment of tuberculosis, evaluating the effectiveness and safety of such pharmacological treatments in terms of cure rate, side effects and effectiveness against resistance mechanisms. The searches were carried out using the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND" through the following search strategy: (tuberculosis) AND ((management) OR (treatment strategy) OR (new drugs)). From this search, 2,126 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in the English language published between 2022 and 2023 and that addressed the themes proposed for this research, review-type studies, meta-analysis, observational studies and clinical trials, available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. A total of 26 articles were selected to compose the present study.

DISCUSSION

Recently, several medications have been studied for the treatment of tuberculosis (TB), aiming to reduce treatment time, minimize side effects, resistance and, mainly, improve patient adherence to the therapeutic regimen. According to World Health Organization data from 146 countries around the world, only 57% of TB patients had successful treatment. A study on TB recurrence after standard treatment showed a two-year recurrence rate of 1.54%. There was no difference between the treatment carried out at 6 months and 9 months, however complete adherence, 100%, reduced the recurrence rate (LEE C. et al., 2023).

According to Lee C. et al. (2023), comparing 100% antibiotic adherence (ATT) with AHR (Adjusted Hazard Ratio) of 1.57 for TB recurrence at two years in patients with 80–89% adherence and 1.63 at 90–99% adherence. The public health strategy may have helped to reduce the recurrence of TB, which has decreased over the years, reducing treatment failures. In previous studies, 9-month treatment demonstrated higher disease recurrence rates compared to 6-month treatment. The association with Cox did not demonstrate a relationship with recurrence.

For Lee C. et al. (2023), what impacts the recurrence of TB is the elimination of non-adherence to DOT (Directly Observed Therapy), which is why carrying out the therapy in a supervised manner is the most impactful point on the outcome of TB. illness.

Another information that draws attention is the impact of non-continued adherence to treatment in the first 180 days, which can generate a window period, allowing the bacteria to become resistant and increasing recurrence to 1.64. It is worth emphasizing that unnecessary interruption of treatment must always be avoided. Men have recurrence rates up to 4 times higher than women. As well as patients with Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD) and cancer are also groups more prone to recurrence. Therefore, greater attention is needed with these groups after the end of treatment (LEE C. et al., 2023).

Furthermore, it is seen that patients with drug-resistant tuberculosis may develop drug hypersensitivity to anti-tuberculous drugs. Based on this, Katran Z.Y. et al. (2023) aimed to determine the demographic and clinical characteristics of patients with resistance to tuberculosis. It was possible to conclude that, of the 25 patients included, there was a

prevalence of hypersensitivity in those with drug resistance of 11.9%, with 48% of the sample being female, with an average age of 38 years. The immediate hypersensitivity reaction is seen in 52% of cases, with maculopapular rashes and urticaria being the most prevalent skin reaction.

Considering that, for many years, conventional tuberculosis treatment was based on a combination of antibiotics (Isoniazid, Ethambutol, Pyrazinamide and Rifampicin), over time new challenges emerged, such as increased drug resistance and side effects. of these, which are considered significant challenges, as they lead to prolonged treatment duration and increased risk of complications and other adverse outcomes. Thus, studies emerged aiming to describe these mechanisms, as well as presenting new possibilities for effective medication regimens to treat the disease. Multidrug-resistant tuberculosis, in particular, poses great challenges to be adequately treated, as it requires prolonged treatment and patient compliance. With longer treatment times, the incidence of adverse reactions also increases. Hypersensitivity to medications, manifesting itself through immediate or delayed reactions, can result in poor adherence to treatment, thus compromising its success. Studies indicated that hypersensitivity reactions occurred with similar frequency in men and women, and the prevalence of hypersensitivity in patients with drug-resistant tuberculosis was 11.9% (KATRAN Z. Y. et al., 2023). Therefore, new drugs were developed and showed effectiveness, such as bedaquiline, which emerged as an option for the treatment of multidrug-resistant and extremely resistant tuberculosis when combined with other drugs, and targets different methods of action of the bacteria, helping to reduce the risk of bacterial resistance.

However, despite its positive effects, the use of the medication was associated with electrocardiographic changes, such as an increase in the QT interval, and secondary cardiotoxic effects (TONG E. et al., 2023).

In 2013, bedaquiline was approved for anti-Tuberculosis (anti-TB) treatment and, in 2019, included as recommendation A by the World Health Organization guidelines for people aged 18 years or older and between 6-17 years (MONDONI M., et al., 2021). Randomized, placebo-controlled clinical trials showed a higher rate of culture conversion and cure within 6 months (MONDONI M. et al.,2021). In 2022, it was approved by the World Health Organization with indications for oral use, prescribed for 9 to 12 months for patients with multidrug-resistant tuberculosis (MDR/RR-TB) (MOTTA I. et al., 2023).

According to Mondoni M. et al. (2021), bedaquiline was also associated with elevated liver enzymes. However, interruption of treatment due to side effects was necessary in only 3.5% of the cases studied. It is, therefore, an option considered safe and well tolerated. Furthermore, studies have described the mechanism of other medications, such as N-acetylcysteine (NAC) used in adjuvant treatment, and even without sufficient literature to definitively prove its action, it was observed that NAC contributed to the improvement of lung function during and after the disease (MAMPAMBA D. A. et al., 2022).

Current recommendations for the treatment of multidrug-resistant tuberculosis and rifampicin according to the World Health Organization include the use of bedaquiline (BDQ) for 6 months or more (TREVISI L. et al., 2023). According to Trevisi L. et al. (2023), since its approval for inclusion in the treatment of patients with multidrug-resistant tuberculosis, bedaquiline has contributed to promoting safer and more effective treatment in rifampicin-resistant (RR) and multidrug-

resistant (MDR) patients. In 2018, the World Health Organization suggested that BDQ be used in individualized regimens with a longer treatment period, between 18 and 24 months, based on a 24-week interval of use. However, in 2020, the World Health Organization updated guidance on the use of BDQ, highlighting that the duration could be safely extended beyond 24 weeks, although it did not provide new guidance on the period of use.

The authors, through a targeted trial, aimed to determine the effect of three BDQ duration treatment strategies (6, 7-11, and >12 months) on the likelihood of treatment success among patients receiving a longer individualized regimen for multidrug-resistant tuberculosis.

Of the 1,468 individuals eligible for the research, it was observed that in patients who received individualized regimens of 18 to 20 months (with a median of four medications), BDQ used for more than 6 months did not improve the likelihood of treatment success above the 85% achieved after 6 months of treatment.

Recommended administration of BDQ was limited to 6 months, both because this was the duration for which it was tested in pivotal trials and because of initial concerns about BDQ's cardiotoxicity. However, subsequent prospective studies have demonstrated that the risk of serious prolongation of the corrected QT interval, arrhythmia, and sudden death is quite low, even when used in combination with other anti-TB drugs that prolong the corrected QT interval. Additionally, the authors point out that they did not find much evidence that BDQ treatment beyond 28 weeks increased the likelihood of treatment success among patients who received longer regimens, which typically consisted of at least four likely effective new and repurposed drugs, such as clofazimine, linezolid and delamanid.

According to Lyons M.A. et al (2022), the treatment of pulmonary tuberculosis (TB) requires combined chemotherapy with at least three drugs and lasting at least 4 to 9 months, and these drug therapies are considered extremely long, toxic and not completely effective. Therefore, new combination regimens as well as new drugs for TB are being investigated. Furthermore, a critical barrier to the codevelopment of tuberculosis regimens is the limited ability to identify optimal drug and dose combinations in early phase clinical trials.

Based on this, Lyons M.A. and colleagues (2022) described a supportive pharmacokinetic and pharmacodynamic model for the killing of the pathogen Mycobacterium tuberculosis during the first 14 days of treatment with the drug regimen bedaquiline-pretomanid-pyrazinamide (BPaZ) in patients adults with pulmonary TB who are susceptible to medications. The authors concluded that pharmacologically, BPaZ is more sensitive to changes in exposure to pyrazinamide and less sensitive (or more robust) to changes in exposure to bedaquiline, with pretomanid being intermediate in these effects. This fact is different from the response seen when these drugs are used in increasing doses in the monotherapy regimen, as can be seen in relation to the efficacy of bedaquiline and a relatively small increase when compared to the use of pyrazinamide.

In parallel with the use of bedaquiline, Larkins-Ford J. and Aldridge B.B. (2022) highlight that its combination with other medications, as evidenced by the Nix-TB and ZeNix-TB clinical trials, demonstrated greater efficacy in the treatment of drug-resistant tuberculosis with the use of pretomanid and linezolid (BPal).

In NiX-TB, linezolid 1,200 mg per day for 6 months was administered to pre-XDR-TB or MDR-TB patients with prior failure for 6 months, and in ZeNix, 600 mg or 1,200 mg per day for 2 or 6 months (LARKINS-FORD,

J.; ALDRIDGE, B. B., 2022). Pretomanid, an inhibitor of mycolic acids, acts as a donor of nitrous oxide, interfering with the replication of mycobacteria, and has also demonstrated effective action when combined with moxifloxacin and pyrazinamide (MONDONI M. et al.,2021).

Medications that focus on inhibiting the synthesis of the M. tuberculosis cell wall have also been studied, presenting a good safety profile. This is the case of the Delamanid and the Pretomanid. The MDR-END trial demonstrated the effectiveness of the use of delamanid, linezolid, levofloxacin and pyrazinamide for 9 to 12 months, with 75% success, similar to the BEAT Tuberculosis trial, which showed efficiency in treatment with the use of bedaquiline, linezolid and delamanida for 6 months (MOTTA I. et al., 2023).

However, the PBal regimen has very low evidence in the World Health Organization recommendations (MOTTA I. et al., 2023). The most common side effects associated with these medications were: nausea, vomiting and QTc interval prolongation.

According to Mondoni M. et al. (2021), a second existing and recently studied medication, from the class of mycolic acid inhibitors, is delamanid, which acts by interrupting cell wall synthesis and has antimycobacterial efficacy against M. tuberculosis, being a medication with little primary resistance and effective with use for 6 months, with a sputum culture conversion rate between 67.6% and 94.4%. However, the World Health Organization classifies delamanid in group C of anti-TB drugs for patients aged >3 years, requiring further studies to recommend it (MONDONI M. et al.,2021). Furthermore, there is Telacebec, which inhibits the mycobacterial cytochrome BC1 complex and, consequently, the production of cellular energy, showing a significant action in reducing the mycobacterial load in sputum. The oral oxazolidinones sutezolid and delpazolide showed the same effect (MONDONI M. et al.,2021).

Some studies discuss new drug administration approaches and host-directed therapies to obtain a more effective drug effect and, mainly, avoid antibiotic resistance (MONDONI M. et al.,2021). According to Mondoni M. et al. (2021), inhaled formulations and nanoparticles are an option for this purpose, as they work by encapsulating medications, in addition to having fewer side effects. Furthermore, vitamin D, metalloproteinase inhibitors and IFN-gamma were shown to be important in increasing macrophage activity, delaying granuloma formation and significantly reducing the production of pro-inflammatory cytokines, respectively (MONDONI M. et al.,2021).

In clinical trials, there was evidence of greater sputum conversion and fever reduction with the use of nebulized IFN-gamma, aerosol, subcutaneously injected IFN-gamma and intramuscularly administered IFN-gamma (ARRIGONI R. et al., 2022).

Regarding CNS involvement, according to Degiacomi G. et al (2022), curcumin, from the polyphenol class, showed significant anti-inflammatory activity, with a reduction in neuroinflammation, through studies in animals infected with TB. However, according to Arrigoni R. et al. (2022), the use of polyphenols in the treatment of TB has not been comprehensively investigated, however, some medications in the class have shown the ability to inhibit the growth and reduce the intracellular survival of M. tuberculosis, such as extracted from Areca catechu and flavonoids, respectively. Furthermore, studies on thiosemicarbazide and granulysin derivatives showed great bacteriostatic action, but present obstacles in their use, such as adverse effects and high manufacturing costs

(DEGIACOMI G. et al., 2022).

Studies with diarylquinoline, AZD5847 (oxazolidinone), PBTZ-169 (benzothiazinone derivative), SQ109 (ethylenediamine—ethambutol analogue), tedizolid (a representative of the oxazolidones), and studies with thioureidoiminomethylpyridinium perchlorate (Tpp) were carried out in Russia with the aim of finding medicines that were effective against TB (STARSHINOVA A. et al., 2022).

According to Starshinova A. et al. (2022), only bedaquiline and delamanid were effective according to the World Health Organization. In Russia, Tpp is used as an effective alternative. The use of bedaquiline had a significant result in increasing the effectiveness of MDR TB treatment, achieving a 61% cure rate. Internationally, it has been demonstrated that linezolid, fluoroquinolones and carbapenems were used concomitantly with bedaquiline.

Regarding the adverse effects and possible disadvantages of bedaquiline, it was noted that 54% of patients presented gastrointestinal disorders and the appearance of cardiac arrhythmias with widening of the QT interval. Another important fact is the low percentage of deaths from the disease, which did not exceed 6.5%, twice lower than compared to international meta-analysis studies (STARSHINOVA A. et al., 2022).

Mudak M. et al. (2023) suggest that a promising strategy to improve TB treatment is to shorten the duration of treatment by introducing more potent antibiotic therapy. Considering the current standard regimen (HRZE) consisting of bedaquiline, pretomanid, linezolid or moxifloxacin. Aiming to reduce treatment time, the study was based on three alternatives: reducing the total dosage, reducing the total number of drugs and replacing it with moxifloxacin. This study was the first to compare regimens with and without moxifloxacin in the search for a result that annihilates granulomas with greater efficiency than HRZE.

Clinical trials resulted in 4 months of treatment with HRZM and RMZE being superior in terms of bactericidal action than HRZE. Thus, demonstrating that moxifloxacin is a promising drug (MUDAK M. et al., 2023).

Studies have also shown that granuloma metabolism reduces with HMZE alone. However, it was found that HMZE has similar efficacy to RMZE in sterilizing granulomas. Aiming to test the effectiveness of treatments containing moxifloxacin, 4-, 3- and 2-way studies of HRZEM were carried out, with the conclusion that all studies that included the drug are more efficient in eliminating low-CFU granulomas than HRZE, while the 3-way is best for high CFU ones. Thus, it was identified that more progressive granulomas are more difficult to treat with fewer antibiotics (MUDAK M. et al., 2023).

It is concluded that a regimen of ZM or EM can result in granulomas with non-eradicated bacteria, which can lead to disease recurrence, due to the fact that moxifloxacin, without association with drugs such as ethambutol and pyrazinamide, is unable to diffuse into the nucleus lacunosum of the granulomas, thus not being fully effective in killing Mtb (MUDAK M. et al., 2023).

Shorter treatment regimens have also been developed, or even the use of conventional medications themselves, such as Rifampicin, but in different doses and dosages. Rifampicin, which is usually used as first line in conjunction with other medications in the conventional treatment of tuberculosis, is related to positive outcomes and shortening the duration of treatment when used in optimized doses (MARTINCZ A. et al.,2023). Furthermore, when using high doses of the medication (40mg/kg/day) instead of standard doses, no drug interactions with other drugs were evidenced. There was little change in

the activities of the studied cytochromes, showing that increasing doses of rifampicin in TB treatment does not seem to impact drug interactions caused by the treatment.

Therefore, current recommendations, based on conventional treatment, can be maintained. Interactions with: caffeine, tolbutamide, dextromethorphan, omeprazole and digoxin were studied. It was also observed that the effect of increasing the dose of rifampicin in relation to the conventional dose was much smaller than the effect of not using rifampicin, in relation to drug interactions. The greatest effect was seen with omeprazole and midazolam (STEMKENS R. et al., 2023). The side effects and the need for more studies to establish better levels of evidence led the World Health Organization to recommend the use of these medications only in research protocols and very specific clinical cases, with serial monitoring with an electrocardiogram. The prolongation of the QTc interval was not enhanced by the association with other drugs such as bedaquiline (MONDONI M. et al.,2021).

In addition to the study of new medications and therapeutic regimens for the treatment of tuberculosis, especially in its multidrug-resistant form, several studies have sought to develop pioneering technologies that, despite still being far from clinical practice, could present revolutionary approaches in the near future. Immunotherapy applied to the treatment of tuberculosis, for example, aims to increase the innate immune response against bacteria in a latent state, reducing the duration of the disease and preventing the development of resistance. The study of macrophage responses to M. tuberculosis could lead to advances in the treatment of TB, through the application of immunotherapy. Target genes were identified based on the properties of sulforaphane (a natural substance found in vegetables such as broccoli) to induce autophagy in macrophages. However, several issues need to be studied until new technologies can generate impacts on clinical practice and global guidelines.

The risk of side effects related to immunotherapy involves, for example, excessive autophagic activation, which can trigger an uncontrolled inflammatory response, worsening the damage caused by TB to lung tissue (XIAO S. et al., 2023).

Finally, among natural medications, probiotics, live microorganisms that improve the intestinal microbial balance, act by improving the host's health by controlling the local immune response, cooperating so that the bacteria do not undergo translocation, in addition to expanding mucosal protection. intestinal, inducing the production of IL-10 (ARRIGONI R. et al., 2022). Among the probiotics studied, according to Arrigoni R. et al. (2022), the probiotic Nyaditum resae® (Nr) stands out, which acts to inhibit the development of active murine TB by intensifying the action of memory TREG cells. In resistant TB, lacticaseibacillus rhamnosus PMC203, found in the vagina of healthy women, proved to be effective in eliminating cells sensitive to the medication. Medicinal plants contain phytochemical elements, such as flavonoids, carotenoids, inols and monoterpenes that have important biotherapeutic capacity in an attempt to replace DOTS which, in addition to having great toxicity, promote reinfection and reactivation of the disease. Researchers are looking for molecules that have the ability to immunomodulate Th1 and Th2, suppressed by infection (GAUTAM S. et al., 2023).

Thus, for Gautam S. et al. (2023), plant-based compounds stand out as potential alternatives to immunomodulation, such as the alcoholic extract of Coleus scutellarioides (Miana leaf), Bergenine, which induces the Th1 and Th7 response and inhibits bacterial

replication. Some of these agents that act as antioxidants and anti-inflammatories can be used as adjuvants to DOTS to control inflammation.

Phytoproducts stand out as a growing alternative in an attempt to alleviate the side effects caused by antibiotics used in the traditional treatment of tuberculosis. Some medicinal plants such as artemisia, myrotahmnus flabellifolius, Carica papaya leaves are used as Ayurvedic treatments according to the patient's tolerance (GAUTAM S. et al., 2023).

According to Romano M. et al. (2023), studies on TB vaccination cover more than 16 different alternatives that are part of the following categories: killed whole cell vaccines, live attenuated vaccines, protein subunit vaccines and viral vector vaccines.

Live attenuated whole cell vaccines, initially developed for pre-exposure, are now being analyzed to prevent TB reinfection. Its advantage lies in the formation of a complex and diverse immune response, providing greater long-term protection. Two examples are VPM1002 and MTBVAC (ROMANO M. et al., 2023).

Inactivated vaccines, such as RUTI, DAR-901 and MIP, were initially developed as pre- and post-exposure, using mycobacteria to act against various Mtb antigens. Viral vector vaccines use viruses (viral vectors), they have limitations due to their immunotoxicity, however, due to their ease in the manufacturing process, they become important in emergency contexts (ROMANO M. et al., 2023).

According to Gautam S. et al. (2023), medications based on liposomes have the ability to encapsulate hydrophilic and hydrophobic compounds, which made it possible to reduce the toxicity of anti-TB drugs in both acute and chronic scenarios of the disease, as evidenced by in vitro and in vivo tests. Test animals carrying the infection that received PZA encapsulated in liposomes and RFB showed complete remission of the bacilli in the lungs, liver and spleen.

Medications based on Nanoemulsions are important alternatives for study due to their thermodynamic stability, high diffusion and absorption rates, among other advantages. Medicines based on solid lipid nanomolecules (SLNs) presented advantages over other drugs due to their more effective encapsulation capacity (GAUTAM S. et al., 2023).

The need for efforts is highlighted in view of the need for therapeutic treatment of latent tuberculous infection (LTBI) and various medication options. For this, Cola J.P. et al. (2023) described a protocol for a clinical trial to evaluate the completion of LTBI treatment with the drug Isoniazid in a 300 mg tablet formulation compared to the use of Isoniazid in a 100 mg tablet formulation, in which the control group received treatment of LTBI with 3 tablets of Isoniazid 100 mg, monitored in month 1, month 2 and at the end of treatment. The primary outcome was completion of treatment, with the ultimate objective of verifying whether the data will provide elements to answer whether isoniazid in the 300 mg formulation reduces non-completion of treatment and whether it is a safe medication for use in patients with LTBI.

Furthermore, it is seen that patients with drug-resistant tuberculosis may develop drug hypersensitivity to anti-tuberculous drugs. Based on this, Katran Z.Y. et al. (2023) aimed to determine the demographic and clinical characteristics of patients with resistance to tuberculosis. It was possible to conclude that, of the 25 patients included, there was a prevalence of hypersensitivity in those with drug resistance of 11.9%, with 48% of the sample being female, with an average age of 38 years. The immediate hypersensitivity reaction is seen in 52% of cases, with maculopapular rashes and urticaria being the most prevalent

skin reaction.

FINAL CONSIDERATIONS

This study provided a detailed analysis of the advances and challenges in the treatment of Tuberculosis, an infectious disease that affects millions of individuals around the world. A critical aspect identified is antimicrobial resistance, which represents a significant percentage among patients. This highlights the importance of developing more efficient therapies and better understanding the benefits and adverse effects of drugs currently used in treatment. Furthermore, the research highlighted the potential of new vaccines under development. These vaccines not only aim to strengthen the host's immune response, but also reduce the incidence of reinfections and prevent antimicrobial resistance. This represents significant hope in the fight against Tuberculosis, as vaccines can become a crucial tool in the intervention and control of the disease. The need for greater attention to the development of more accurate and rapid diagnostic methods was highlighted, essential for the timely and effective treatment of Tuberculosis, especially in cases of drug resistance. Furthermore, the importance of public health education and prevention strategies to reduce the spread of the disease was emphasized. The urgency to address Tuberculosis in a holistic manner stands out, considering both therapeutic advances and prevention and control strategies. The development of new therapies and vaccines, along with continued efforts in research and public health, is vital to address the challenges presented by Tuberculosis and improve health outcomes for affected patients globally.

REFERENCES

ARRIGONI R. et al. Antibiotic Resistance to Mycobacterium tuberculosis and Potential Use of Natural and Biological Products as Alternative Anti-Mycobacterial Agents. **Antibiotics**. v.11, p.1431, 2022.

COLA, João Paulo et al. Protocol for pragmatic randomized clinical trial to evaluate the completion of treatment of latent Mycobacterium tuberculosis infection with Isoniazid in the 300 mg formulation. **PLoS ONE**, v. 18, n. 2, p. e0281638, 2023.

DARTOIS, Véronique A.; RUBIN, Eric J. Anti-tuberculosis treatment strategies and drug development: challenges and priorities. **Nature Reviews Microbiology**, v. 20, n. 11, p. 685-701, 2022.

DEGIACOMI, Giulia et al. New Drugs and Novel Cellular Targets against Tuberculosis. **International Journal of Molecular Sciences**, v. 23, n. 22, p. 13680, 2022.

DIRIBA,G. et al. Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis. **International Journal of infectious Diseases**, v.132, p.50 - 63, 2023

GAUTAM, Silvi et al. Medicinal Plants as Therapeutic Alternatives to Combat Mycobacterium tuberculosis: A Comprehensive Review. **Antibiotics**, v. 12, n. 3, p. 541, 2023.

HALEY, Connie A. et al. Implementation of bedaquiline, pretomanid, and linezolid in the United States: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant tuberculosis disease. **Clinical Infectious Diseases**, v. 77, n. 7, p. 1053-1062, 2023.

KATRAN, Zeynep Yegin et al. Drug hypersensitivity in drug-resistant tuberculosis. **World Allergy Organization Journal**, v. 16, n. 5, p. 100778, 2023.

LARKINS-FORD, J.; ALDRIDGE, B. B. Advances in the design of combination therapies for the treatment of tuberculosis. **Expert Opinion on Drug Discovery**, v. 18, n. 1, p. 83–97, 2022.

LEE, Chung-Shu et al. The incidenc of tuberculosis recurrence: Impacts of treatment duration of and adherence to standard anti-tuberculous therapy. **J Infect Public Health**, v.16, n.11, p. 1778-1783, 2023.

LIEBENBERG, Dale et al. Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. **Frontiers in Cellular and Infection Microbiology**, p. 1443, 2022.

LYONS, Michael A. Pharmacodynamics and Bactericidal Activity of Combination Regimens in Pulmonary Tuberculosis: Application to Bedaquiline-Pretomanid-Pyrazinamide. **Antimicrobial Agents and Chemotherapy**, v. 66, n. 12, p. e00898-22, 2022

MAHAPATRA, Biswajit et al. Cost effectiveness of decentralized care model for managing multi-drug-resistant tuberculosis in low-and middle-income countries: a systematic review protocol. **JBI Evidence Synthesis**, p. 10.11124, 2023.

MAPAMBA, Daniel Adon et al. Impact of N-acetyl cysteine (NAC) on tuberculosis (TB) patients—a systematic review. **Antioxidants**, v. 11, n. 11, p. 2298, 2022.

MARTINECZ, Antal et al. High rifampicin peak plasma concentrations accelerate the slow phase of bacterial decline in tuberculosis patients: Evidence for heteroresistance. **PLoS Computational Biology**, v. 19, n. 4, p. e1011000, 2023.

MONDONI, Michele et al. Novel treatments in multidrug-resistant tuberculosis. **Current Opinion in Pharmacology**, v. 59, p. 103-115, 2021.

MOTTA, I. et al., Recent advances in the treatment of tuberculos**is. Clinical Microbiology and Infection**, v.1198, n. 743, p.339-7, 2023.

MUDAK M. et al. Optimizing tuberculosis treatment efficacy: Comparing the standard regimen with Moxifloxacin-containing regimens. **PLoS Computational Biology**. v.19, n.6, 2023.

PATON, Nicholas I. et al. Treatment strategy for rifampin-susceptible tuberculosis. **New England Journal of Medicine**, v. 388, n. 10, p. 873-887, 2023.

ROMANO, Maria et al. A structural view at vaccine development against M. tuberculosis. **Cells**, v. 12, n. 2, p. 317, 2023.

STARSHINOVA, Anna et al. Efficacy of tuberculosis treatment in patients with drug-resistant tuberculosis with the use of bedaquiline: the experience of the Russian Federation. **Antibiotics**, v. 11, n. 11, p. 1622, 2022.

STEMKENS, Ralf et al. Drug interaction potential of high-dose rifampicin inpatients with pulmonary tuberculosis. **Antimicrobial Agents and Chemotherapy**, p. e00683-23, 2023.

TONG, Enyu et al. The efficacy and safety of bedaquiline in the treatment of pulmonary tuberculosis patients: a systematic review and meta-analysis. **Antibiotics**, v. 12, n. 9, p. 1389, 2023.

TREVISI, Letizia et al. Effectiveness of bedaquiline use beyond six months in patients with multidrug-resistant tuberculosis. **American Journal of Respiratory and Critical Care Medicine**, v. 207, n. 11, p. 1525-1532, 2023.

WARNKEN, Zachary et al. Development of low-cost, weight-adjustable clofazimine mini-tablets for treatment of tuberculosis in pediatrics. **European Journal of Pharmaceutical Sciences**, v. 187, p. 106470, 2023

XIAO, Sifang et al. Identifying autophagy-related genes as potential targets for immunotherapy in tuberculosis. **International Immunopharmacology**, v. 118, p. 109956, 2023.