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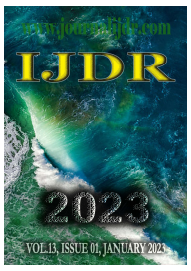

REVIEW ARTICLE OPEN ACCESS

NEW DRUGS FOR THE TREATMENT OF TUBERCULOSIS PULMONARY: INTEGRATIVE LITERATURE REVIEW

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ABSTRACT

Objective: The main this article is to bring the main studies about the new treatments for pulmonary tuberculosis, in 2018 to 2022. ***Methods:*** An integrative literature review was carried out, synthesizing the results and studies in progress about new drugs anti-tuberculostatic in the treatment of sensitive e resistant pulmonary tuberculosis. ***Results:*** The 24 articles and 14 studies were selected and referred exclusively treatments for pulmonary tuberculosis. The results reflect that it is not possible to reduce the treatment to period shorter, more effective regimens an widely distributed to vulnerable people. ***Final Considerations:*** In Brazil, the unified health system (SUS) can garantees completely the treatment of sensitive and resistant tuberculosis. The regimen used in Brazil is recommended by the WHO, is the most effective and in association of antibiotics, as recommended by recent studies.

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INTRODUCTION

Tuberculosis (TB) is a serious infectious disease, transmitted through droplets, caused by Mycobacterium tuberculosis (SILVA *et al*, 2018; SOARES L *et al*, 2020). According to the World Health Organization (WHO), this disease exceeds the number of cases of infection and death by the HIV virus. In addition, it was the second disease that kills the most globally, caused by a single infectious agent, after COVID-19 (BRASIL, 2021). Another relevant concern is the high number of underreported cases (MONTIEL I *et al*, 2020). Due to the COVID-19 pandemic, tuberculosis services were hampered by the interruption of access to treatment and diagnosis. As a result, there was a decrease in notifications and an increase in deaths from tuberculosis in 2021 (PAI M *et al*, 2022). Due to the number of new reported and underreported cases, the search for new tuberculostatic drugs is still an important issue (GŁÓWKA *et al*, 2018). The TB chemotherapy process, which began in the 1940s, underwent changes and combinations over the years, due to the evidence of resistance of the strains to drugs (DA SILVA Jr, 2020).

The initial pharmacological treatment measure for TB, until the 1960s, lasted 24 months. After the introduction of ethambutol and the triple regimen, the treatment lasted 12 months (BALLESTERO J *et al*, 2020). With the discovery of rifampicin in 1971, the treatment time was reduced to 6 months, in addition to the creation of a set of strategies to promote adherence to treatment, which involved the organization of the health system, control over the dispensing of medicines, supervision and monitoring of treatment by the public health service (BALLESTERO J *et al*, 2020). The current regimen recommended by the WHO lasts at least 6 months, and despite being resolute, contributes to non-adherence and loss of continuity of MDR-TB treatment (DA SILVA Jr, 2020). In addition to patient-centered interventions, new drugs have been developed, tested and adapted so that there is an average reduction of one third of treatment time (AMARAL, 2019). Among these, we have delamanid - a drug approved and included in the treatment of tuberculosis in 2014 and bedaquiline - approved in 2019 (AZIMKA, 2017; SILVA *et al*, 2020). Due to the global burden of tuberculosis, shorter treatment regimens with existing or reused drugs are needed to help control the disease. The standard tuberculosis treatment regimen currently recommended

by the WHO consists of a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol and then a 4-month continuation phase with isoniazid and rifampicin. The development of effective, safe and shorter treatment regimens for Sensitive Tuberculosis (TBS) and Multidrug-resistant Tuberculosis (MRTB) could significantly improve tuberculosis management and treatment success rates (ROSSATO SILVA *et al*, 2020). Tuberculosis treatment in Brazil is part of a government operation for the TB control program, which offers treatment free of charge to all diagnosed patients (BRASIL, 2020), and exclusively controlled by the SUS. To date, for countries such as Brazil, the most cost-effective strategy is the prevention of transmission of multidrug-resistant pathogenic microorganisms, which is associated with primary health care (DA SILVA Jr, 2020). Thus, this research work seeks to carry out an integrative review regarding the development, evaluation and validation of new drugs for the treatment of tuberculosis, in order to contribute to a comprehensive analysis of their implementation in an efficient and safe way. And in this way, direct the academic community to reflect on the reasons related to the choice and effectiveness of these drugs, by the Unified Health System (SUS), in the control and treatment of TB.

MATERIALS AND METHODS

This article is an integrative literature review, carried out with the objective of synthesizing the current sources of research on new drugs used in the treatment of pulmonary tuberculosis, and providing evidence for the basis of new studies on this topic. Because it is a study that presents a bibliographic survey on the subject addressed, recent scientific works were analyzed, from the year 2018 to 2022, which report on studies on new tuberculostatics that provide theoretical and methodological basis in the development of this research. For the preparation of this study, data collection was performed by searching for scientific articles found in the following databases: Publications of Medical Literature Analysis and Retrievel System Online (PUBMED), Scientific Electronic Library Online (SciElo), Cochrane Library Online and N.I.H. National Library of Medicine (Clinical Trials.com). In the field of data search, keywords such as “pulmonary tuberculosis”, “tuberculostatics”, “treatment” and “drugs” were used, so that relevant articles and clinical trials on the topic could be found. Inclusion criteria for this study were studies published in the years 2018 to 2020, which discussed new drugs used in the treatment of pulmonary tuberculosis on the aforementioned platforms, and their possible forms of treatment. The included articles are available in Portuguese and English. Articles published before 2018 were excluded from this study. Also, articles on preventive measures and treatments in special conditions (pregnancy, children and adolescents), and with diseases associated with tuberculosis (liver diseases, kidney diseases, diabetes and infection) were excluded. by HIV). Of the articles selected for reading the abstract, result and conclusion, those that did not mention drugs registered or used without association with standard treatment for sensitive, resistant and multidrug-resistant pulmonary tuberculosis were excluded. The selected articles were stored in the Mendeley Reference Manager platform, the main findings were inserted into tables in the Word Microsoft 365 program, and later analyzed and described for discussion and conclusion of this research.

DISCUSSION

Diarylquinoline, Bedaquiline (Sirturo®): Bendaquiline (Sirturo ®) is indicated in appropriate combination for the treatment of multidrug-resistant pulmonary tuberculosis (MDR-TB), rifampicin-resistant tuberculosis (RR-TB), multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (BRAZIL, 2020). Bedaquiline belongs to the diarylquinoline class, whose mechanism of action specifically inhibits mycobacterial ATP synthase (adenosine 5-triphosphate), an essential enzyme for energy generation in Mycobacterium tuberculosis. The molecular mechanisms of microbacterial resistance suggest that resistance to bedaquiline includes modification of the atpE target gene (ROSSETTI *et al*, 2002). In Brazil, the Coordination Of Monitoring And Evaluation Of Health Technologies (CONITEC) recommends Sirturo® in the treatment of patients with rifampicin-resistant, multidrug-resistant and extensively drug-resistant tuberculosis, under the Direct Observation Treatment (TOD) strategy. The total duration of treatment with Sirturo® is 24 weeks (BRASIL, 2020). The systematic review retrieved 2 studies carried out between 2018 and 2022. The first, (NCT04087759), in Phase 1, is characterized as an open randomized crossover study in healthy adult subjects to assess the relative oral bioavailability and food effect of tablets of 100 mg of bedaquiline administered as different test formulations compared to the commercial tablet formulation (F001). However, this study has not produced results so far. The other study found (NCT03896685) is a Phase III, randomized, controlled, open-label, multi-country study that seeks to assess the efficacy of new combination regimens for the treatment of fluoroquinolone-resistant MDR-TB. Until the conclusion of this research, this study is in the recruitment phase. Still from the same study, the regimens examined combine newly approved drugs bedaquiline and delamanid with existing drugs known to be active against Mycobacterium tuberculosis (linezolid and clofazimine). Previous studies show significant results of fixed effects that favor the use of bedaquiline compared to treatment without the use of bedaquiline, making it recommended by CONITEC since 2020 (BRASIL, 2020).

Imidazopyridine Amide

Telacebec (Q203): Telacebec (Q203; TCB) consists of a molecule containing an imidazo [1,2-a] pyridine-3-carboxamide (IPA) structural motif, and has become the third new class of modern drugs with proven antituberculosis activity (MALIK I *et al*, 2021). After diarylquinoline bedaquiline and nitroimidazoles, delamanid and pretomanid (SILVA D *et al*, 2018). Recent clinical trials developing Telacebec (Q203) are performed under a pan-tuberculosis regimen, without distinction between drug-sensitive and drug-resistant tuberculosis (DE JAGER V *et al*. 2020). The mechanism of action of Telacebec (Q203) targets the cellular energy production of Mycobacterium tuberculosis by inhibiting the mycobacterial cytochrome bc1 complex. In vitro, the depletion of ATP synthesis resulted in cell death, regardless of the bacterial replication status (PETHE K., 2013). As of January 2021, Telacebec was also involved in phase II clinical trials focused on the treatment of Coronavirus Disease-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (MALIK I *et al*, 2021). For the preparation of this article, 4 clinical trials involving this drug were found, between 2018 and 2022. The first clinical trial of dose escalation in humans (PMID: 34694872), was characterized as a randomized, placebo-controlled, double-blind, in which it was performed to assess the safety, tolerability and pharmacokinetics of Telacebec® in the body. A total of 56 healthy subjects of both sexes were included in this study, and 42 active and 14 placebo were determined. In all subjects treated with Telacebec (10 to 800 mg), good tolerance was observed and there were no significant or serious adverse events. After a single oral administration of telacebec (10 to 800 mg), the maximum plasma concentration (Cmax) reached averaged 2.0 to 3.5/h and showed a multiexponential decline (WANG J *et al*, 2021). The same study continued as the first Phase 1A randomized, placebo-controlled, double-blind, dose-escalation clinical trial in humans, in which it demonstrated a significant increase in plasma concentrations observed in the fed condition compared to fasting condition, with a mean geometric ratio of 3.93 Cmax. It was possible to observe a moderate delay in T max (4.5 h) in the fed condition (KIM J *et al*, 2022). Such results support the investigation of the use of TCB for the treatment of tuberculosis.

Prior to this study, completed in 2018, we found the trial (NCT03563599), Phase IIa, open and randomized, involving 60 patients who had never undergone treatment, in which smear positive with drug-sensitive pulmonary TB to assess the early bactericidal activity of Telacebec® (Q203), patients were assigned to receive 14

days of oral Telacebec® at a dose of 100 mg, 200 mg or 300 mg once daily or combination therapy with rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE). As a result, increasing doses of Telacebec® were associated with greater reductions in viable mycobacterial sputum load (DE JAGER V *et al*. 2020). A study to evaluate the biomarker change, efficacy, pharmacokinetics, safety and tolerability of Telacebec® in a patient with Covid-19, (NCT04847583), phase 2, randomized controlled, open label, to determine the effects of TCB in inhibiting the production of leukotrienes, clinical change, pharmacokinetics and safety in participants with moderate disease of COVID-19, still does not have results found, although it has completed status in the databases.

Nitroimiidazole

Delamanid: Delamanid (Deltyba-) is a non-mutagenic nitroimidazooxazole (or nitroimidazopyran) with early bactericidal activity. Nitroimidazole is a nitroimidazo-oxazole derivative that acts as an inhibitor of mycolic acid biosynthesis, thus interrupting cell wall metabolism and facilitating better drug penetration into anaerobic mycobacteria, heterogeneous variants of M. Tuberculosis, as it inhibits the synthesis of ketomycolic acids. and methoxylic. (BLAIR *et al*, 2018). Delamanid is indicated as part of an appropriate combination regimen in adult patients with pulmonary MDR-TB when an effective treatment regimen cannot be composed due to resistance or tolerability. The recommended dose in adults is 100 mg twice daily, with a recommended treatment period of 24 weeks. Delamanid tablets should be taken orally, with food, administration by TOD is recommended as a strategy (BRASIL, 2020). About this drug, 3 clinical trials were found carried out in the period selected for this study. The first trial (NCT01571414), published in 2018, sought to assess the safety and tolerability of PA-824, a bicyclic nitroimidazole, when combined with efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r). These drugs are used to treat HIV infection, or rifampicin (RIF), used to treat tuberculosis. This study seeks to assess drug interactions for safety, tolerability and pharmacokinetics (PK) between PA-824 and EFV, LPV/r or RIF. The results of this trial have not yet been published. Also included in this study was a multicenter, open-label, multi-arm, randomized, controlled, phase II-III Pragmatic Clinical Trial (NCT02589782) to evaluate a more effective and less toxic MDR-TB Treatment Regimen (TB-PRACTECAL) . This trial seeks to evaluate short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs for the treatment of biologically confirmed multi-drug resistant TB (MDR-TB TB). For (SILVA D *et al*, 2018) it is estimated that approximately 700 patients underwent treatment with delamanid in 2017, either through the Médecins sans Frontières (Doctors without Borders) projects or the compassionate use program of the European Respiratory Society/TB Consilium from WHO. A new trial (NCT05382312), started in 2022, aimed to measure early bactericidal activity, safety, tolerability and pharmacokinetics with GSK3036656 - a compound with a new mechanism of action under development for MTB, in which it selectively inhibits the Leucy t- ribose nucleic acid RNA synthase - in combination with delamanid or bedaquiline, delamanid in combination with bedaquiline or standard of care for 14 days in participants with newly diagnosed sputum smear positive, sensitive pulmonary tuberculosis. Participants will revert to standard care (RIFAFOUR® e-275) once study treatment (Day 1 to Day 14) is complete. The main objective of this study is to dose escalation and establish the anti-tuberculosis effect of GSK3036656, in serial colony forming units (CFU) MTB counts in sputum over 14 days of therapy, in association with the drugs currently used in the treatment, such as delamanid and bedaquiline.

Oxazolidinone

Linezolid

Sutezolid

Delpazolide (LCB01-0371): Oxazolidinone is a heterocyclic organic compound mainly used as an antimicrobial agent. This class of antimicrobials is active against a wide spectrum of Gram-positive bacteria, including methicillin resistant ones (LAG CHO, 2020). Oxazolidinones have as a mechanism of action the inhibition of protein synthesis, however, in a different stage from that inhibited by other antimicrobials. In this way, there is no cross-resistance with macrolides, streptogramins or even aminoglycosides. Linezolid, an oxazolidinone, inhibits the 50S subunit of the ribosome in protein synthesis, demonstrates efficacy. However, its toxicity profile limits its use beyond resistant tuberculosis (SILVA D *et al*, 2018). Sutezolid and delpazolid are two newer generation oxazolidinones used in early clinical trials and are expected to be as effective as linezolid and less toxic. The efficacy and superiority of sutezolid over linezolid was also observed in phase I clinical trials. The recruitment phase for phase II clinical trials is currently ongoing During the search for trials carried out between 2018 and 2022 on these drugs, 2 articles were found that addressed oxazolidinone-linezolid in the treatment of pulmonary tuberculosis. The clinical trial started in August 2021, (NCT05007821) aims to assess efficacy and tolerability - whether participants discontinue treatment, due to side effects of a drug or treatment period - this study performs a short-term antiretroviral regimen. -TB comparing two doses of linezolid (LZD), combined with bedaquiline (BDQ), delamanid (DLM) and clofazimine (CFZ). It will also measure the level of these drugs in the participants' blood. As a secondary endpoint, the study will also assess the safety (the level and type of side effects from a drug or treatment) of the combination of these drugs. The results of this study are expected for the year 2024.

According to the study (NCT05040126), from 2021, partial results performed with Linezolid demonstrate similar bactericidal activity over 14 days, regardless of the single daily dose or twice-daily doses. And it suggests that a single daily dose will increase patient compliance and reduce total exposure time to drug concentration that is greater than the calculated concentration associated with mitochondrial toxicity (probable mechanism for the toxicities of peripheral neuropathy and myelosuppression). Sutezolid is in phase 2a of testing, Phase 1a being concluded only recently (NCT03199313), due to licensing problems, it still does not present published results. The trial (NCT03959566) is an open-label, randomized, controlled, multicenter Phase IIB dose-seeking clinical trial to evaluate the safety, tolerability, pharmacokinetics, and exposure-response relationship of different doses of sutezolid (STZ) in combination with bedaquiline, delamanid, and moxifloxacin in adults with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary tuberculosis. Participants will be randomized to one of five arms containing bedaquiline, delamanid, and moxifloxacin with different doses of STZ (0mg, 600mg once daily (OD), 1200mg OD, 600 mg twice daily (BD), 800 mg BD). The duration of study treatment will be three months, followed by a 2-week follow-up period. The results of this study are scheduled for August 2022. Delpazolid is an antibiotic that targets Gram-positive bacteria (MRSA, VRE), including M. tuberculosis (LAG CHO *et al*, 2020). No recent ongoing studies with delpazolid were found. Previous studies, performed in a phase 2 clinical trial for oral (PO) administration and a phase 1 trial for intravenous (IV) administration to treat Gram-positive bacteremia (MRSA, VRE), applied cyclic amidrazone blocks applied to the scaffold delpazolid key, and showed greater advantage associated with delpazolid due to its safety. In phase 1a of a phase 1 clinical trial to evaluate its safety, 64 subjects were divided into eight groups, six of which received delpazolid and two who received placebo. The study was the first double-blind, randomized human trial of delpazolid. To administer ascending single doses (SADs), delpazolid was administered in steps of 50 mg up to 3200 mg. Only mild adverse events were observed up to 2400 mg. At a delpazolid dose of 3200 mg, adverse events related to the gastrointestinal (GI) tract were observed. In the 3200 mg dose group, volunteers had to ingest 16 tablets of 200 mg delpazolid at one time, resulting in GI-related adverse events. Therefore, the maximum tolerated dose of delpazolid was determined to be 2400 mg per day. A phase 1b study was conducted based on ascending multiple doses (MADs) over seven days. Thirty-two subjects were divided into eight groups, six of which received delpazolid and two of which received

placebo. Subjects received delpazolid in MADs of 400 mg BID (bis in die, twice daily) to 1600 mg BID for seven days. Doses of up to 1200 mg BID for seven days were well tolerated with no specific adverse events noted. Following the 7-day MAD study, a 21-day MAD study was conducted to assess bone marrow toxicity, which is one of the most critical side effects of linezolid. Subjects given delpazolid 800 mg once daily (QD) to 1200 mg BID were monitored for up to three weeks to more accurately assess adverse events such as myelosuppression, as signs such as decreased platelet counts may be seen even after two weeks. In summary, no adverse events related to myelosuppression or serious adverse events were observed in phase 1a with SADs up to 2400 mg and in phase 1b with MAD up to 1200 mg BID (2400 mg daily) for 21 days. Therefore, delpazolid does not appear to have adverse events associated with repeated dosing. Furthermore, delpazolid did not cause problems with CYP-mediated metabolism and cardiac repolarization (LAG CHO *et al*, 2020).

Benzothiazinone: Benzothiazinone (BTZ) is a class of antituberculosis agents effective against multidrug-resistant Mycobacterium tuberculosis strains (PATELA *et al*., 2020). This drug acts by interfering with cell wall synthesis, inhibiting the DprE1 enzyme responsible for the conversion of deccaprenyl-phosphoryl-ribose to decaprenyl-phosphoryl-arabinose, which is an enzyme involved in the biosynthesis of arabinos, which are precursors of bacterial cell wall components (REIS AND CONCEIÇÃO, 2013/ LECHARTIE, 2012), the irreversible inhibition of this enzyme is responsible for its antimicrobial action through the enzyme-target mechanism, thus making this drug a great tool to control the creation of antimicrobial resistance. In this way, BTZs act in the same way as other drugs available on the market and already used as the first-line anti-TB drug, such as isoniazid (INH) (PATELA *et al*., 2020; AJMAL *et al*, 2021). Treatment schemes are still under analysis, however it is possible to demonstrate that they have significant anti-tubercular activity, both for in vitro and in vivo studies (AJMAL *et al*, 2021). These studies demonstrate two main forms of administration, oral and pulmonary - designed by inhalation - and yet, each with its research variations (PATELA *et al*., 2020; AJMAL *et al*., 2021; HOELSCHER 2019). Until then, there are ongoing studies that mainly aim at the adequacy of single and multiple dosages of BTZ043, which still do not present results that can be evidenced and declared (HOELSCHER 2019). On the other hand, research still in vitro and in vivo with tests in mice, which take into account the tests that are based on the application of BTZ in the pulmonary form, showed that through coadjuvants and/or with the aid of plasmatic proteins there are a significant increase in antimicrobial effects, since BTZ has very low aqueous solubility. In this way, it is possible to obtain significant reductions in the bacterial load. The treatment protocol is being analyzed to verify which schemes should be applied. Currently, there are studies that follow both in vitro lines and in vivo lines, however, most follow without a final result.

Riminophenazine: The main representative of the Riminophenazine group is Clofazimine, originally used for the treatment of leprosy (SILVA D *et al*, 2018). Although it has little bactericidal activity, recent studies show that there is an important reduction in the time of the therapeutic plan (SOUZA, 2019), clofazimine is recommended by the WHO and the American Thoracic Society for patients with rifampicin-resistant Tb (ABDELWAHAB *et al*, 2020). Clofazimine still does not have a very well elucidated mechanism of action, what is known is that it targets the outer membrane, the bacterial respiratory chain and the transport of ions, in addition to these, some points are known, such as adverse effects and components with a high propensity to drug interactions that make it need and demand studies, which mainly seek the dose-exposure relationship and response in patients with resistant TB (ABDELWAHAB *et al*, 2020/ SILVA DR *et al*, 2018). Given the current shortage and the epidemiological reality in which the world finds itself, the need for a more viable treatment is perceived, ongoing studies seek mainly to verify which plans to use, among others, clofazimine as a component of the therapeutic scheme and what needed to get the answer. To carry out this study, we did not find results to elucidate about Riminophenazine during the selected period.

CONCLUSION

Only 2 studies related to the use of Bedaquiline were found, where the first one did not present results so far and the second one is in the recruitment phase. However, previous studies have demonstrated its efficacy compared to treatment without the use of bedaquiline. Regarding Telacebec, 4 clinical trials were found, where the first demonstrated a significant increase in plasma concentrations observed in the fed condition compared to the fasting condition, a result that supports the investigation of the use of Telacebec for the treatment of tuberculosis. Another trial evaluated the early bactericidal activity of Telacebec, finding that administration of increasing doses of the drug was associated with greater reductions in viable mycobacterial sputum burden. Another study evaluated the change in biomarkers, efficacy, pharmacokinetics, safety and tolerability of Telacebec in patients with covid-19. It also sought to determine the effects on the inhibition of leukotriene production, clinical alteration, pharmacokinetics and safety in participants with moderate covid-19 disease. However, it has no results found although it has a completed status. Delamanid was the drug used in 3 clinical trials. The first sought to evaluate drug safety, tolerability and pharmacokinetic interactions between PA – 824 and EFV, LPV/r or RIF, but the results of this trial were not published. Another study evaluated early bactericidal activity, safety, tolerability and pharmacokinetics with GSK3036656 in combination with delamanid or bedaquiline, reverting to standard care once study treatment was completed. The approach to treatments with oxazolidinone-linezolid was found in 2 clinical trials. One of them, started in August 2021, evaluated the tolerability of a short-term treatment comparing two doses of LZD, combined with BDQ, DLM and CFZ. It will also evaluate the safety of the combination of these drugs. The results of this study are scheduled for 2024. Another trial, in 2021, using linezolid showed similar bactericidal activity over 14 days.

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