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Cyclooxygenase-2 as potential intervention target of leprosy reactions: a systematic review



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ABSTRACT

Background: Leprosy reaction is an acute inflammatory of leprosy complication that potentially cause disability. Prompt and appropriate treatment is needed to prevent this permanent neurological complication. As inflammation of this reaction is mediated by cyclooxygenase-2 (COX-2), therefore targeting this substance may potential to prevent disability. This systematic review aimed to define COX-2 as a potential target of intervention in leprosy reaction.

Method: Medline, Cochrane library, PubMed, and Google scholar databases were searched for articles published at any time. Observational study and clinical trial, comparative, prospective, retrospective, and descriptive study were extracted, analyzed, and discussed.

Results: We found 6 studies that met the inclusion and exclusion criteria, with 104 participants with leprosy reactions and 143 comparators included in this review. In leprosy reactions, COX-2 expression was found in the vessels and nerves of the dermis and subcutis. Macrophages are cell mostly abundantly expressing COX-2. The COX-2 expression was found higher in the leprosy reaction compare to the non-leprosy reaction. Genetically, genes PTGS2 and TNFAIP6 encode COX-2 production also tend to increase especially in type 1 reaction.

Conclusions: Preclinically and genetically, COX-2 is a potential target for intervention of leprosy reaction.

Keywords: COX-2, cyclooxygenase-2, leprosy, reaction.

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INTRODUCTION

Leprosy is a high-morbidity neuro-dermatologic disease caused by *Mycobacterium leprae*.¹ A complex complication with difficulties in the clinical management of this disease is leprosy reactions.¹⁻³ These reactions are characterized by acute inflammatory episodes, which are precipitated by pharmacology and non-pharmacology. Therefore, it can occur before, during, or after complete treatment.² It's about 50% of leprosy patients develop this immune-mediated complication.⁴

Two types of leprosy reactions are known, categorized as type 1 reactions (T1R) or reversal and type 2 reactions (T2R) or erythema nodosum leprosum (ENL).⁵ The T1R is a cell-mediated immunity reaction that leads to skin or nerve inflammation at the infection site. The lesion becomes erythema and edema, paraesthesia, pain, tenderness, or sudden deterioration of its function.^{3,6} Meanwhile ENL is immune complex-mediated, which is characterized by diverse

symptoms such as painful, erythematous subcutaneous nodules associated with fever, lymphadenitis, neuritis, arthritis, orchitis, or iridocyclitis. In some cases, ENL may develop into a chronic or recurrent course leading to neuropathy and disability.³

Both reactions potentially cause nerve damage and leads to disabilities. But, prompt and appropriate treatment significantly prevents this permanent neurological complication. As observed in TR1, 60-70% of cases recover after being treated within six months of onset.⁵ Classically, a corticosteroid is the standard treatment for this condition. However, the optimal dose and duration of treatment remain unclear.^{7,8} In addition, chronic course and recurrences occurred in 62,5% of patients.^{9,10} So, a new modality with better performance is needed to manage this reaction.

Inflammation of this reaction is mediated by various substances including cyclooxygenase-2 (COX-2). Some studies revealed increase expression of COX-2 in

lesions, micro-vessels, nerve bundles, and nerve fibers.^{11,12} Therefore, this enzyme may be a new insight target of treatment. The objective of this study is to review COX-2 as potential in managing leprosy reactions.

METHODS

Two researchers conducted the literature search independently, and any doubts and disagreements were solved by negotiation with the corresponding author. The data search on Medline, Cochrane library, PubMed, and Google scholar for articles published any time using keywords 'Cyclooxygenase-2' AND 'leprosy' AND 'reaction' OR 'reversal' OR 'erythema nodosum leprosum'. The criteria of the studies included in the review were as follows: an observational study and clinical trial, a comparative, prospective, retrospective, and descriptive study reported in English. Duplicate publications, reviews, and animal research were excluded (Figure 1).

RESULTS

The online literature search resulted in 57 citations (Figure 1), 6 studies met the criteria and were included in this review. The total sample size was 104 subjects with leprosy reactions and 143 comparators. Each study includes between 6 to 57 subjects for the case and 6 to 90 subjects for comparators. All studies were comparative studies (Table 1).

The COX-2 expression in leprosy disease and leprosy reactions may be observed in several types of tissues. In leprosy reactions, especially T1R, COX-2 expression was found in the vessels and nerves of the dermis and subcutis. Vessel type mostly expressing COX-2 is microvessels which contributed to vascular dilation and tissue edema. Nerve bundles and isolated nerve fibers were also distinctly positive for COX-2.¹¹ Vascular endothelial growth factor (VEGF) inducing prostaglandin (PG) production through COX-2 stimulation and PG synthase

expression was also upregulated.¹³ The pro-inflammatory products leukotriene B4 (LTB4), prostaglandin D2 (PGD2) and lipoxin A4 (LXA4) catalyzed by COX-2 are also increased in T1R.¹² This causes vascular changes leading to tissue edema in T1R and potential nerve damage.¹³

Specific cell analysis, studies on lepromatous lesions, and tuberculoid leprosy found most positive COX-2 cells

were macrophages and occasionally immunostained in fibroblasts and endothelium (seen only 3-4%).¹⁴ The study of Malhotra et al., using skin biopsy specimens, found that COX-2 expression was higher in the leprosy reaction than without either reaction only in dermal macrophage cells while in vascular endothelium was not different. According to the type of reaction, T1R had higher

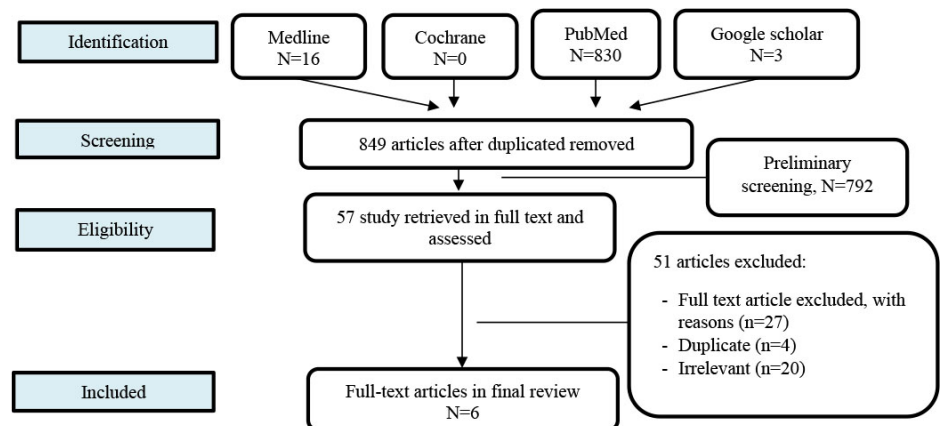


Figure 1. Flow chart study selection process.

Table 1. Studies found analyzed in the review

Author, year	Study design	n	Finding
Pesce, Grattarol, Menini, & Fiallo, (2006)	Comparative study of skin biopsy findings between patients with RR (six BT and one BL) and BT patients (three BL and four LL) without reactionary leprosy.	7 T1R patients and 7 comparators	Only T1R showed additional COX-2 expression in microvessels and nerve bundles and isolated nerve fibers. The same sites also express vascular endothelial growth factor (VEGF). Possibly a relation between VEGF and COX2 expression, with VEGF enhancing prostaglandin production through COX2 stimulation and prostaglandin synthase expression.
Malhotra, Suvirya, Malhotra, Kumar, Kumar, Husain (2021)	Case-control study evaluating expressions of <i>Cyclooxygenase 2</i> and <i>Vascular Endothelial Growth Factor</i> in skin biopsies.	57 cases and 90 controls	Both COX-2 and Vascular Endothelial Growth Factor (VEGF) expression were significantly higher in type 1 reaction followed by type 2 reaction as compared to controls.
Silva, Webb, Andre, Marques, Carvalho, de Macedo, Pinheiro, Sarno, Pessolani, & Belisle, (2017)	Comparative study of a patient with and without T1R by metabolomics-based analyses via liquid chromatography-mass spectrometry	7 patients T1R and 9 comparators	Proinflammatory leukotriene B4 (LTB4), prostaglandin D2 (PGD2), and lipoxin A4 (LXA4) in patients with T1R were significantly increased. Theoretically, PGD2 production is catalyzed by COX-2.
Orlova, Cobat, Thu Huong, et al, (2013)	A retrospective study comparing gene set signature between T1R and non T1R	6 T1R patients and 6 non-T1R patients	<i>PTGS2</i> , encoding COX-2 preferentially upregulated genes in the T1R gene set signature. In addition, <i>TNFAIP6</i> highly expressed in the early onset T1R samples, encoded <i>TNF-stimulated gene 6 (TSG6)</i> .
Kiszewski, Becerril, Baquera, Ruiz-Maldonado, Hernández Pando, (2003)	A comparative study comparing COX-2 expression between LL and TL leprosy patients.	20 LL leprosy and 20 TL leprosy	Dominant COX-2-positive cells identified were macrophages located in the papillary dermis, reticular dermis, and peri adnexal. The COX-2 was significantly higher in LL than in TL ($P < 0.001$)
Fiallo, Clapasso, Favre, Pesce (2002)	A comparative study comparing VEGF produced through COX-2 between T1R and non-T1R leprosy	7 T1R and 14 comparators	Vascular endothelial growth factor (VEGF) induces prostaglandin (PG) production through COX-2 stimulation and PG synthase expression. This causes vascular changes leading to tissue edema in T1R and potential nerve damage.

COX-2 macrophage levels than T2R, leprosy without reaction, and healthy control ($p < 0.001$). Based on their treatment status, patients who were on medication had a higher risk of COX-2 expression than non-on-treatment patients (191.50 ± 56.76 vs 141.98 ± 78.85).¹⁵

Genetic studies have also shown that the PTGS2 gene (central gene in the Arachnoid Acid Pathway) encoding COX-2 is up-regulated in T1R patients. In addition, the TNFAIP6 gene encodes TNF-stimulated gene 6 (TSG6), whose function as an inducer of COX-2 expression in macrophages is also upregulated in early-onset T1R.¹⁶

DISCUSSION

Management of leprosy reactions is still a challenge because it is a chronic disease and often recurs. If not managed properly, there is a risk of nerve damage which in turn causes disability. Various pathways have been identified to underlie this reaction, one of which is the pathway that requires COX-2 involvement. In this review, it was found that increased COX-2 expression was associated with leprosy reactions, especially T1R. So it has the potential to be a therapeutic target.

The cyclooxygenase enzyme is a substance that plays a role in catalyzing the conversion of cell membrane arachidonic acid to prostaglandins and leukotrienes. There are two types of COX that are often known, namely COX-1 and COX-2. The COX-1 enzyme is found in almost all tissues and is produced during inflammation. While COX-2 is induced only in response to inflammatory stimuli.^{15,17} Therefore, targeting COX-2 selectively in the management of leprosy reaction may be safe without affecting constitutive body homeostasis.

Given that leprosy reactions can occur before, during, or after treatment,² identification of COX-2 is also important in patients who are not on treatment as a basis for prevention. The study found that lepromatous leprosy patients had a strong COX-2 expression, while healthy controls were weakly expressed.¹⁸ Based on the Ridley-Jopling classification, BB, BL, and LL tend to show higher COX-2 expression. Thus, these types may provide a better advantage with the administration of

COX-2 inhibitors.¹⁴⁻¹⁵ COX-2 acts through an increase of prostaglandins.¹⁴ This also explains that T1R is rare in type LL because in this type COX-2 macrophages are higher. COX-2 reduces T cell activity through intermediate mediators such as prostaglandin E-2 (PGE-2) and interleukin 10 (IL-10). These intermediate mediators down-regulate CD4 helper T cells and then decrease cell-mediated immunity.^{14,19-20} Other pro-inflammatory mediators such as leukotriene B4 (LTB4), prostaglandin D2 (PGD2) and lipoxin A4 (LXA4) also contributed in this reaction. Those all of their production need COX-2.¹² Given that, the administration of COX-2 inhibitors has the potential to prevent or reduce leprosy reactions.

Prostaglandin E-2 produced through COX-2 is also associated with increased VEGF.²¹ The VEGF-1 is a growth factor that centrally mediates vascular permeability and dilatation as seen in T1R.¹⁷ Research on cancer reveals that COX-2 inhibitor concomitant with VEGF inhibitor improves the outcome compared to anti-VEGF alone.²² But our review found that one study reveals VEGF is overexpressed in T1R¹³ meanwhile another study found nondifference of VEGF in T1R compared to non-T1R.¹⁵ Therefore, the role of COX-2 in T1R through this VEGF pathway is controversial.

Genetically, T1R patients carry different genes, especially in the arachidonic acid metabolism pathway. This pathway is important in the inflammatory process. This review found that the PTGS2 gene encodes COX-2 and the TNFAIP6 gene encodes TNF-stimulated gene 6 (TSG6), whose function in COX-2 induction is upregulated.¹⁶ The results of this study are supported by the study of Mindrescu et al. which found that COX-2 expression was increased by the induction of TSG-6 protein in macrophage cells.²³ These findings provide preferential administration of COX-2 inhibitors in patients with this genetic predisposition to prevent leprosy reactions.

Based on this review, COX-2 has the potential to become a target of therapy, but all studies found in this review only focused on analyzing its pathways. Unfortunately, no interventional study using COX-2 inhibitors was found, either

pre-clinic or clinical experimental. That means a further preclinical and clinical study using COX-2 inhibitor is needed to confirm and weigh the safety and cost-effectiveness of the drug as a prevention or treatment of leprosy reaction.

In addition, COX-2 has become a widely targeted treatment for several diseases such as osteoarthritis, rheumatoid arthritis, antipyretics, and analgesics. Several COX-2 inhibitors are known, including non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. But in general, this drug acts as an anti-inflammatory and analgesic. However, it should be noted that this drug also has side effects such as gastrointestinal bleeding and ulceration, impaired renal function, and inhibition of platelet aggregation.²⁴⁻²⁷

CONCLUSION

Pre-clinically, COX-2 is a potential target in managing leprosy reactions. The COX-2 expression increases in macrophage cells of nerves and vessels. The COX-2 expression is more significant in T1R compared to T2R. Genetically, gene-encoding COX-2 production tends to increase in T1R.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest regarding this publication.

AUTHOR CONTRIBUTIONS

Author LMMR contributes to systematic review concept and proofread of the manuscript. Author LGMPs contributes in manuscript construction, literature research, and translation.

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