

EFFECTIVENESS OF CYCLOPHOSPHAMIDE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Cyclophosphamide (CFM) is an alkylating agent of the oxazaphosphorine class, widely used in the treatment of multiple pathologies, including systemic lupus erythematosus (SLE), which is a chronic, autoimmune, inflammatory, systemic disease with no cure. **Objective:** To compare the efficacy of cyclophosphamide in the main manifestations of systemic lupus erythematosus (SLE). **Method:** This is a systematic review of the literature, in which data were collected from a bibliographic search of databases. The inclusion criteria for articles were the use of the descriptors "Systemic Lupus Erythematosus" AND "Cyclophosphamide" AND "Efficacy" AND "Contraindications," as well as articles in English or Portuguese from studies published between 2000 and 2024. **Results:** When analyzing the efficacy of CFM in SLE presentations, we noted that in patients with proliferative glomerulonephritis (PNG), the superiority of cyclophosphamide use is evident when compared to the isolated use of corticosteroids (CS), as well as in the treatment of lupus nephritis (LN), where the addition of cyclophosphamide to corticosteroid therapy improved the renal condition of patients and reduced the risk of renal failure. In addition to its use in renal manifestations, CFM can be used in the treatment of neuropsychiatric, cardiovascular, and pulmonary manifestations. **Conclusions:** CFM as a choice with level A recommendation and evidence for proliferative nephritis; level B in myelopathy and membranous nephritis; level C in acute pneumonitis, pulmonary hemorrhage, interstitial lung disease, and pulmonary hypertension; and level D in refractory pericarditis.

Keywords: Systemic Lupus Erythematosus; Cyclophosphamide; Efficacy; Contraindications.

INTRODUCTION

Cyclophosphamide (CFM) is a drug that acts both as an antineoplastic and an immunomodulator, as it is an alkylating agent of the oxazaphosphorine class, which is widely used in the treatment of multiple forms of cancer, autoimmune diseases in adults and children, and also in some dermatological diseases. Its dosage has a wide range and can be administered either orally (PO) or intravenously (IV), with the route, dosage, and duration of treatment being determined by the disease in question (FERNANDES, 2008).

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, inflammatory, systemic disease with no cure. It is more prevalent in women between the ages of 20 and 40, especially in countries with greater exposure to sunlight.

(SOUZA; SANCHES, 2021;). Signs and symptoms include kidney changes (lupus nephritis being one of the most common), changes in the musculoskeletal system, vasculitis, serositis, pneumonia, dermatological involvement, endocarditis, and neuropsychiatric manifestations (WALLACE; GLADMAN, 2020).

The use of cyclophosphamide in SLE is based on its ability to destroy B and T cells and suppress antibody production. It is being tested with other drugs, including glucocorticoids, to develop a better treatment plan for patients (MACEDO, 2020). The Systemic Lupus Erythematosus Consensus determines CFM as the choice with level A recommendation and evidence for proliferative nephritis; level B for myelopathy and membranous nephritis; level C for acute pneumonitis, pulmonary hemorrhage, interstitial lung disease, and pulmonary hypertension; and level D for refractory pericarditis (BORBA, 2008).

Thus, the present study aims to compare the efficacy of cyclophosphamide in the main manifestations of systemic lupus erythematosus (SLE).

METHODOLOGY

This is a systematic review of the literature, in which data were collected from a bibliographic search of the following databases: Virtual Health Library (BVS), Public Medlines (Pubmed), Scientific Electronic Library Online (SciELO), UpToDate, and Latin American and Caribbean Health Sciences Literature (LILACS).

The inclusion criteria for articles were the use of the descriptors "Systemic Lupus Erythematosus" AND "Cyclophosphamide" AND "Efficacy" AND "Contraindications"; as well as articles in English or Portuguese, from studies published between 2000 and 2024, addressing the use of the drug and the efficacy of its use. The exclusion criteria were unpublished theses and dissertations, duplicates, and articles indexed in databases other than those established.

RESULTS

For a better understanding of the use of CFM in the various presentations of SLE, topics related to the main systems of the human body will be discussed according to the data in the literature.

RENAL MANIFESTATIONS

In patients with proliferative glomerulonephritis (PGN), the superiority of cyclophosphamide use is evident when compared to the isolated use of corticosteroids (CS), since its prolonged use was more effective in maintaining renal function and reducing the recurrence rate, especially in patients with some severity criteria (MAGALHÃES; DONADI; LOUZADA JR, 2003).

In addition, in patients with GNP and severity criteria, we should consider MFC as the first option, considering availability, absorption, and tolerance to medications and adherence to treatment. However, in women, the use of CFM for longer than 6 months may induce ovarian failure, depending on the age at which medication was started, the duration of treatment, and the cumulative dose (KLUMB, 2015).

Regarding the treatment of lupus nephritis (LN), it was noted that the addition of cyclophosphamide to corticosteroid therapy improved the renal condition of patients and reduced the risk of long-term renal failure when compared to the use of corticosteroids alone, especially in patients with proliferative LN (DIAS FILHO; MITUIASSU, 2022). However, other studies have revealed that mycophenolate mofetil (MMF) may be more effective than cyclophosphamide for some groups of patients and is currently also considered a first-line therapy for the treatment of class III, IV, and V LN (MEIRELES, 2013).

In addition, cyclophosphamide has been tested as an alternative to leflunomide in the treatment of proliferative lupus nephritis (PLN), as its use in combination with glucocorticoids has yielded results similar to standard treatments. The reduction of anti-dsDNA autoantibodies and proteinuria decreased significantly after treatment with the two drug classes combined (MACEDO, 2020).

One of the main regimens used to reduce the adverse effects of CFM during treatment for LN is the Euro-Lupus Regimen, which has proven that low-dose CFM IV allows for results comparable to those obtained with high-dose regimens, with the added benefit of a lower cumulative dose of cyclophosphamide and fewer adverse effects (MEIRELES, 2013).

CARDIOVASCULAR MANIFESTATIONS

One of the most severe complications of SLE is myocarditis, which causes great concern when there is no improvement with standard medications, thus requiring the use of CFM for refractory cases (BORBA, 2008).

NEUROPSYCHIATRIC MANIFESTATIONS

Cyclophosphamide plays a comprehensive role in the treatment of neuropsychiatric issues arising from SLE, in doses that vary according to severity, combined with medications for the type of manifestations presented. One of the manifestations is myelopathy, which should be treated with pulse therapy with corticosteroids combined with IV CFM (SATO, 2004).

PULMONARY MANIFESTATIONS

In patients with interstitial lung disease or pulmonary hypertension due to SLE, oral cyclophosphamide or monthly pulse therapy usually leads to stabilization and, in some cases, even improvement of the pulmonary condition (BORBA, 2008). Among the rarest but most concerning manifestations of pulmonary involvement in SLE are acute pneumonitis and pulmonary hemorrhage, in which pulse therapy with corticosteroids alone or in combination with CFM is the first line of treatment (BORBA, 2008).

CONCLUSION

In the present study, we presented the main uses of CFM for the treatment of SLE, with its efficacy in the treatment of lupus nephritis being noteworthy. However, many studies have not yet confirmed with complete certainty the benefits of this drug (either as monotherapy or in combination), and many of them have shown significant limitations. Therefore, due to the scarcity of studies

on this topic, more studies are needed to demonstrate the efficacy of cyclophosphamide for SLE, with long-term follow-up and a more satisfactory sample size, to better elucidate its safety and best indications, so that we can increasingly improve the clinical condition of lupus patients and reduce its side effects.

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