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Review Article

Bromocriptine in Rheumatic Diseases: A Review

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Abstract

Hyperprolactinemia is frequent in rheumatic diseases. Bromocriptine (BRC) is an antagonist of prolactin and was studied in a few rheumatic diseases with controversial results. The aim of the present study was to review articles on BRC in rheumatic diseases. Articles on lupus, rheumatoid arthritis, psoriatic arthritis (PsA), and reactive arthritis were found. Fourteen articles were found. In lupus, 5 articles evaluated BRC in a 2.5-7.5 mg/day dosage. The follow-up varied from 6 to 14 months. They showed improvement in lupus disease activity (Lupus Disease Activity Index or Lupus activity measure scores) in 4/5; a trend was verified in another article, 1/5, and one study evaluated improvement in the mood of the systemic lupus erythematosus patients. In RA, there are 4 articles with 119 patients. The BRC dosage ranged from 5 mg/day to 10 mg TID. About 2/4 of the articles showed improvements [morning stiffness and Health Assessment Questionnaire (HAQ)], and 2/4 did not show any difference. Regarding PsA and reactive arthritis, 5 articles with 43 patients were found. The BRC dose varied from 2.5 to 30 mg/day. All studies showed improvements of the studied diseases. Side effects were mild and infrequent. In conclusion, BRC seems to be efficacious in a few rheumatic diseases (lupus, PsA, RA, and Reiter's), with mild side effects. Future studies with a larger number of participants and in other rheumatic diseases are needed.

Keywords: Bromocriptine, prolactin, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, rheumatic diseases, systemic lupus erythematosus

Key-messages

- Prolactin seems to be increased in several rheumatic diseases and BRC is its pharmacological antagonist.
- Bromocriptine is able to improve disease activity in lupus, RA, PsA, and reactive arthritis.

Introduction

Prolactin (PRL), a hormone primarily associated with lactation, is produced by the pituitary gland.[1] Interestingly, PRL receptors are also present on immune cells, where the hormone exerts significant immunomodulatory effects. Prolactin can stimulate the activity of B and T lymphocytes, suppress natural killer cell function, and enhance the production of cytokines such as interleukins (ILs) 2, 4, and 6.[1] Hyperprolactinemia (HPRL), an elevated level of PRL, is linked to several autoimmune disorders, including lupus, RA, scleroderma, and myositis, among others.[2]

Bromocriptine (BRC), a dopamine agonist substance, selectively blocks PRL secretion and is primarily used to treat prolactin-secreting pituitary tumors.[3] Recent studies have explored the potential therapeutic effects of BRC in autoimmune rheumatic diseases, suggesting it may offer benefits in this context. It is important to note that cabergoline is a novel anti-PRL drug more commonly used than BRC although few article are available in the rheumatology field.

Therefore, the aim of the present study was to review the studies on BRC in rheumatic diseases.

Methods

This systematic review was conducted in accordance with internationally recognized guidelines for systematic reviews, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. The literature search was performed across 3 major databases: PubMed, Scielo, and Web of Science, covering the period from 1966 to May 2024. No language restrictions were applied.

Search Strategy

The search terms included: "bromocriptine" AND "rheumatic diseases" OR "rheumatoid arthritis" OR "systemic lupus erythematosus" OR "psoriatic arthritis" OR "vasculitis" OR "spondylarthritis" OR "Reiter disease" OR

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"reactive arthritis" OR "myositis" OR "antiphospholipid syndrome" OR "Sjogren's syndrome." These terms were selected to maximize sensitivity and specificity, ensuring the inclusion of relevant studies.

Inclusion Criteria

Inclusion criteria include studies involving adult patients (age ≥18 years); diagnosis of rheumatic disease based on internationally recognized criteria, such as American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) guidelines; and prospective studies investigating BRC as a treatment for rheumatic diseases.

Exclusion Criteria

Exclusion criteria include narrative or systematic reviews, editorials, case reports, or case series; preclinical studies, including in vivo and in vitro research; studies involving pediatric populations or non-rheumatic conditions.

Study Selection and Data Extraction

Articles identified during the search were initially screened by title and abstract to determine eligibility. Full-text articles of potentially relevant studies were subsequently reviewed. Two independent reviewers conducted the screening and data extraction to minimize bias. Discrepancies between reviewers were resolved by consensus or consultation with a third reviewer.

Extracted Data

The extracted data include sample size and demographic characteristics of participants; diagnosis of the rheumatic disease; dosage and duration of bromocriptine therapy; methods used to assess outcomes, such as disease activity indices (e.g., SLEDAI, SLAM, and HAQ) and clinical parameters; and reported adverse events.

Results

Figure 1 shows the flowchart of the included articles.

Main Points

- Hyperprolactinemia is frequent in rheumatic diseases and BRC is used as the prolactin antagonist.
- This article reviewed the studies on BRC in the following rheumatic diseases: lupus, RA, PsA, and reactive arthritis.
- Bromocriptine was able to improve disease activity of all studied diseases with absent or mild adverse events.

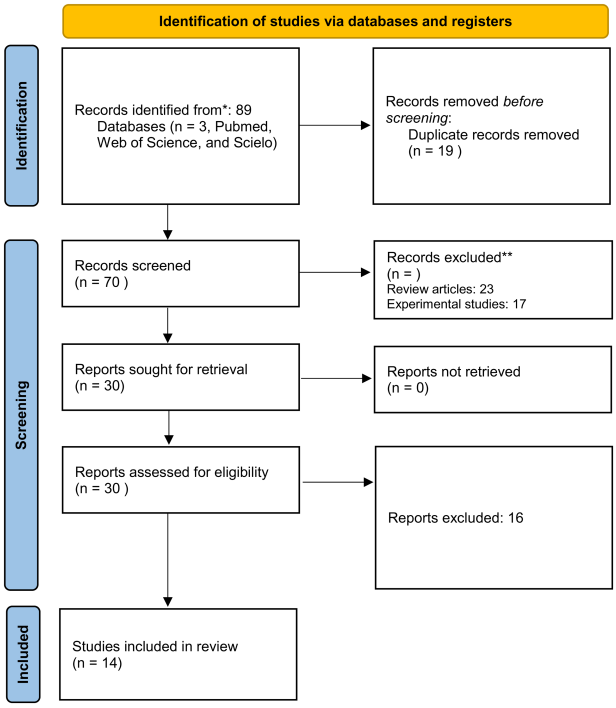

Figure 1. Flowchart of the included studies.

Table 1 summarizes the studies of BRC in systemic lupus erythematosus.[4-8] Five articles were found, including 179 patients. The countries in which the articles were produced were Mexico (n = 2), China (n = 1), and the United States (n = 2). One study was a double-blinded, controlled, and randomized trial; 3 were prospective and 1 was a prospective controlled one. Age ranged from 26.8 ± 3.7 to 31 ± 9.4 years old, and female sex varied from 57% to 100% in the articles included. The disease duration varied from 3.25 ± 1.9 years to 6.3 ± 5.1 years. The dosage of BRC varied from 2.5 to 7.5 mg/day. Follow-up in all studies ranged from 6 to 14 months.

Concerning outcomes, the articles showed improvement in lupus disease activity (SLEDAI and/or SLAM scores) in 4/5; a trend was verified in another article, 1/5, and one study evaluated improvement in the mood of the systemic lupus erythematosus (SLE) patients. One study observed a decrease in anti-dsDNA antibodies. In addition, the side effects were present in 1/4 articles and were all mild, absent or equal to controls in 2/4 studies, and not described in 1/4 articles.

Table 2 shows the studies of BRC in RA.[9-12] Four articles were found, including 119 patients. The countries in which the articles were produced were Chile (n = 1), France (n = 1), Iran (n = 1), and Israel (n = 1). Three studies had a prospective design, and one was a case series. Age varied from 46.1 ± 13 to 59.7 ± 8.1 years old, and female sex varied from 82.5% to 100% in the articles included. The disease duration ranged from 8.9 ± 0.5 years to 11 ± 8.1 years. The BRC dosage ranged from 5 mg/day to 10 mg TID. The follow-up ranged from 3 to 12 months.

Concerning outcomes, 2/4 of the articles showed improvements (morning stiffness and Health Assessment Questionnaire-HAQ), and 2/4 did not show any difference. Concerning adverse effects, 3/4 showed their presence, and all were mild and characterized by náusea.

Table 3 shows the studies of BRC in PsA and reactive arthritis.[13-17] Five articles were found, including 46 patients. The countries from the selected articles were France (n = 1), Germany (n = 2), Israel (n = 1), and Mexico (n = 1). The BRC dosage ranged from 2.5 mg/day to 30 mg/day. The follow-up ranged from 3 to 4 months. Concerning outcomes, all studies showed improvements of the studied diseases.

Discussion

Bromocriptine has been studied in lupus, RA, PsA, and reactive arthritis, with good results and mild adverse effects in most cases.

Hyperprolactinemia has been documented in various rheumatic diseases. Our research group investigated HPRL across several autoimmune conditions and demonstrated it in 24% of polymyositis subjects, in 21% of lupus, in 6% of RA patients, and in 3% of systemic sclerosis.[2] Bromocriptine, a prolactin receptor antagonist,

Table 1. Studies on Bromocriptine in Systemic Lupus Erythematosus

Author, Reference	Study Design	Country	N, Age, Gender	Disease Duration	Bromocriptine Dosage	Follow-up	Outcome	Side Effects
Qian et al., 2015[4]	Open prospective trial	China	76 30.47 ± 4.33 yo 100% females	3.27 ± 0.91 years	2.5 mg twice a day for 14 days after delivery	12 months	BRC reduced SLEDAI and reduced the need for immunosuppressants.	3 had mild vertigo and nausea
Jara et al., 2007[5]	Prospective controlled trial	Mexico	20 26.8 ± 3.7 yo 100% females	3.25 ±1.9 years	2.5 mg/day plus prednisone 10 mg/day vs prednisone 10 mg/day from 25 to 35 weeks of pregnancy	Monthly during pregnancy and 1 month postpartum	A trend of reduction in lúpus flares and less premature membrane rupture in the BRC group	None
Walker et al., 2000[6]	Open-label prospective	United States	10 ND 57% females	ND	1.25 mg/day and 2.5 mg/day after 1 week. Subsequent increase until 3.75 - 7.5 mg/day	6 months	BRC reduced SLAM and SLEDAI scores. BRC improved 2/4 mood scales (Anxiety Scale and Anger ± Hostility Scale)	ND
Alvarez-Nemegyeii et al., 1998[7]	Double-blind, randomized, placebo-controlled study	Mexico	66 31.5 ± 9.4 yo 97% females	6.3 ± 5.1 years	2.5 mg/day vs placebo	12 months	BRC reduced the SLEDAI score and the mean number of flares/patient/month	Equal to control
McMurray et al., 1995[8]	Open-label prospective	United States	7	NA	NA	14 months	BRC reduced SLAM and SLEDAI scores, as well as anti-dsDNA antibodies.	NA

BRC, bromocriptine; N, number; ND, not described; SLE, systemic lupus erythematosus; yo, years old; NA, not available.

Table 2. Studies on Bromocriptine in Rheumatoid Arthritis

Author, Reference	Study Design	Country	N, Age, Gender	Disease Duration	Bromocriptine Dosage	Follow-up	Outcome	Side Effects
Salesi et al., 2013[9]	Prospective double-blinded trial	Iran	89 46.1 ± 13 yo 82,5% females	ND	5 mg/day vs. placebo	3 months	.No difference in RA disease activity.	Mild nausea and sleep disturbance
Dougados et al., 1998[10]	Prospective trial	France	6 57.5 ± 9.9 yo 83% females	11 ± 8.1 years	1.25 mg/day and increased to 6.25 mg/day	12 months	No differences, except 1/6 could reduce cyclosporin dose.	3/6 had nausea and discontinued BRC
Figueroa et al., 1997[11]	Open prospective controlled trial	Chile	9 59.7 ± 8.2 yo 100% females	8.9 ± 0.5 years	10 mg TID (mean dose 19.7 mg/day)	3 months	BRC improved morning stiffness, HAQ. BRC reduces the proliferative response of peripheral blood mononuclear cells to phytohaemagglutinin and *Candida albicans*.	Most patients had nausea, and 1 stopped BRC.
Mader et al., 1997[12]	Case series	Israel	5 35-50 yo ND	ND	5 mg/day	6 months	BRC improved disease activity in 2/5 patients at 6 months	ND

BRC, bromocriptine; N, number; ND, not described; RA, rheumatoid arthritis; yo, years old.

Table 3. Studies on Bromocriptine in Psoriatic Arthritis and Reiter Disease

Author, Reference	Study Design	Country	Disease	N, Age, Gender	Disease Duration	Bromocriptine Dosage	Follow-up	Outcome	Side Effects
Weber and Frey, 1987[13]	Case series	Germany	Psoriatic arthritis	4 Mean: 45 yo 75% females	Mean: 11 years	20 to 30 mg/day	Mean: 3 months	BRC improved all cases with complete remission.	ND
Weber and Frey, 1986[14]	Case series	Germany	Psoriatic arthritis	35 ND	ND	2.5 mg up to 30 mg/day	xx	BRC ld to 77% of significant remission, 34% total remission, and 43% remission of approximately 50% of the articular symptoms	ND
Buskila et al., 1991[15]	Case report	Israel	Psoriatic arthritis	1 Female	ND	ND	ND	Remission of skin and arthritis after BRC	None
Eulry et al., 1995[16]	Case series	France	Psoriatic arthritis	2	ND	ND	ND	All patients improved	xx
Bravo et al. 1992[17]	Case series	Mexico	Reiter disease	4 ND 100% males	ND	2.5-5 mg/day	4 months	All patients improved	ND

BRC, bromocriptine; N, number; ND, not described; RA, rheumatoid arthritis; yo, years old.

is primarily utilized to manage HPRL secondary to pituitary tumors.[19] Given the association between HPRL and certain rheumatic conditions, the therapeutic potential of BRC to inhibit prolactin has been explored in the context of these diseases, as highlighted in the present review.

Blank et al[18] demonstrated that BRC therapy combined with cyclosporine is able to decrease antinuclear autoantibody titers in uveitis patients, independent of PRL levels. Moreover, experimental studies have shown that BRC exhibits immunosuppressive effects on B and T lymphocytes. These effects include the suppression of early B cell proliferation and differentiation, as well as the inhibition of IL-1 synthesis.[19,20] In another study, BRC therapy initiated the production of nonspecific T suppressor cells and reduced in vivo autoantibody synthesis in animal models of lupus and antiphospholipid syndrome.[21]

Prolactin is essential for IL-1-dependent lymphoid cell proliferation and stimulates regulatory enzymes involved in nitric oxide synthesis, which are elevated in RA patients.[22]

Recent advances in the understanding of HPRL in autoimmune diseases highlight the intricate relationship between prolactin and pro-inflammatory cytokines such as IL-6, IL-17, and tumor necrosis factor-α. These cytokines, which are key drivers of autoimmune pathogenesis, appear to be modulated by prolactin through its receptor-mediated activation of the JAK–STAT signaling pathway. This interaction promotes an inflammatory milieu, exacerbating disease activity in conditions such as lupus and RA. Studies have shown that targeting this prolactin–cytokine axis could offer a dual approach to reducing systemic inflammation and controlling autoimmunity.

Additionally, the role of prolactin in the differentiation and survival of Th17 cells has gained attention in recent years. Th17 cells, known for their contribution to chronic inflammation and tissue damage in autoimmune diseases, are influenced by prolactin-induced pathways. Experimental data suggest that reducing prolactin levels through agents like bromocriptine may decrease Th17-mediated inflammation, offering a novel therapeutic avenue. These findings underscore the need for further research into the cellular and molecular mechanisms underlying prolactin's role in autoimmunity, which could pave the way for more targeted and effective therapies.

The findings of this systematic review support the notion that BRC holds promise as a therapeutic option for autoimmune diseases, including RA, lupus, and PsA.

The article's strengths include the comprehensive search for all rheumatic diseases treated with BRC, and the inclusion of diverse study designs, with the exception of review articles, editorials, and experimental studies. The patients included fulfilled the international criteria for rheumatic diseases.

Some limitations identified include the small number of participants in the studies. Additionally, large-scale prospective, double-blind trials are necessary to validate these findings.

In conclusion, this review identified 14 articles on BRC in rheumatic diseases (SLE, RA, PsA, and RD). This drug appears to be effective in most diseases, with mild adverse events. However, future studies are needed to evaluate additional rheumatic conditions and include larger cohorts of participants.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

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