The Role of Corticosteroids along with Other Therapies in Treating Idiopathic Granulomatous Mastitis: A Narrative Review

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ABSTRACT

**Background:** The use of oral corticosteroids to treat idiopathic granulomatous mastitis (IGM) has been a point of controversy for a long time. In addition, a wide diversity of combinations with other therapies have been reported so far. This study aims to review the usage of oral corticosteroids and their combinations in the published literature.

**Methods:** PubMed and Scopus were searched using the key word “granulomatous mastitis.” Citations were filtered in two stages, considering the titles/abstracts and full texts. Papers reporting the treatment of IGM with corticosteroids with/without other treatments were included.

**Results:** Fifty-eight citations were included in this study, 31 of which had at least a group of patients treated only with systemic corticosteroids. Combination therapy of systemic steroids with immunosuppressants, surgical interventions, and antibiotics were used in 6, 12, and 13 studies, respectively.

**Conclusion:** Considering the inconsistency of studies in reporting the severity of the disease, administered treatments, outcome of treatment, side effects, and follow-up, our study failed to provide solid evidence for using corticosteroids as the first step in the management of idiopathic granulomatous mastitis. There is still a need for further studies emphasizing the homogenization of such reports. In this regard, preparing a questionnaire to help homogenize future reports on IGM is highly recommended.

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM), first described by Kessler and Wolloch, is a nonmalignant inflammatory disease of the breast that most commonly presents with a palpable breast mass and pain, and can mimic breast carcinoma. It is often seen in Turkish, Iranian, Indian, and Chinese women and at childbearing age.

Since the clinical and radiologic findings can be inconclusive, histopathology is the optimal tool for establishing the diagnosis. It is necessary to exclude the other causes of granulomatous inflammation of...
the breast, for instance, acid-fast bacilli, foreign body, and fungal causes.\textsuperscript{4,5}

Currently, there are few agreed-upon guidelines explaining the treatment of choice for IGM. In this regard, surgical (such as mastectomy, excision, and drainage) and non-surgical management (such as corticosteroids and antibiotics) have been explored so far.\textsuperscript{2,6} Other treatment options are topical steroids and immunosuppressants such as methotrexate and azathioprine.\textsuperscript{7,8}

Researchers have investigated the effectiveness of corticosteroids alone and in combination with other therapies, such as surgery,\textsuperscript{9} and immunosuppressants.\textsuperscript{8} It is thought that oral steroids can be effective for non-surgical management.\textsuperscript{10} However, adverse events reported for corticosteroid treatment make it a challenging choice for physicians.\textsuperscript{11,12} A systematic review showed that surgical interventions lead to a more rapid remission and a higher remission rate than corticosteroids; however, surgical procedures may cause stress and concern about scars and deformity and may not always be cost-effective.\textsuperscript{6} Therefore, the role of corticosteroids in the treatment of IGM is yet to be fully understood.

This study aims to review the use of systemic corticosteroids, alone or in combination with other therapies, for the management of patients with IGM. In addition, the quality of relevant reports is evaluated in order to address their heterogeneity or homogeneity.

METHODS

A literature search of PubMed and Scopus was conducted with the search term “granulomatous mastitis.” These databases were searched from inception to August 2021. We manually reviewed the retrieved articles. Papers that complied with the following conditions were included: 1) presenting any patient with granulomatous mastitis, 2) mentioning the treatment modality used for management, and 3) the use of corticosteroids for at least one treatment group. The study was excluded if its language was not English or if the full text was unavailable. A charting table was developed by the research team, which included the study and study characteristics, age of patient(s), initial treatment(s), dosage, duration, recurrence rate, follow-up period, outcome, and treatment selection criteria. If more than one initial treatment was used, the data of each arm was charted in separate rows, called “treatment group.” Two reviewers (AM and SM) extracted the data independently from the full texts of the articles included. The reviewers discussed the arising conflicts until a consensus was reached. The uncertainties were resolved by consulting the expert authors (AK and NM). Whenever possible, numerical data was extracted in order to provide descriptive analysis. Multiple virtual meetings were held by the authors to discuss plans, extracted data, and controversial articles.

RESULTS

Fifty-eight records were ultimately included in the analysis.\textsuperscript{4,7-10,13-64} The included studies had been conducted in 17 different countries, the most frequent of which was Turkey (N=18). The studies had been conducted between 1992 and 2021. The most frequent study designs were case reports and case series (N=29), followed by cross-sectional studies (N=20), clinical trials (N=3), cohorts (N=3), and case-control studies (N=3). The weighted mean age of the patients participating in these studies was 34.22.

The methods used for biopsy to establish the diagnosis, from the most to least frequent, were core needle biopsy (N=34), incisional biopsy (N=16), excisional biopsy (N=14), fine-needle aspiration biopsy (N=6), and frozen section (N=1). As some studies used more than one mode of biopsy to reach the final diagnosis, the total frequency of each biopsy modality was 71 and more than the number of studies included in this review.

The reported side effects of corticosteroids included Cushing’s syndrome, weight gain, dyspepsia, skin acne, hair loss, hyperglycemia, hirsutism, striae, mood disturbances, hyperprolactinemia, headache, gastrointestinal problems, mild blurred vision, and skin lesion.

The treatments administered for the patients were classified into five groups as follows: 1) Only corticosteroid therapy, 2) Corticosteroid therapy plus antibiotics, 3) Corticosteroid therapy plus immunosuppressant drugs, 4) Corticosteroid therapy plus surgery, or 5) Other treatments. Findings in each treatment group will be discussed in the following sections (Table 1).

Only Corticosteroids

In 31 studies,\textsuperscript{4,7-10,15,17,18,23,29,31,34-36,38,41-45,47,48,51,53,56-59,62} at least one group of patients were treated by only prescribing corticosteroids (359 patients in 32 treatment groups in total). The research methodology was of case report, cross-sectional, case-control, clinical trial, and cohort types, used in 14, 12, 2, 1, and 2 studies, respectively. Corticosteroids were in the form of prednisolone, methylprednisolone, and topical steroid. The mean dosage of the prescribed prednisolone and methylprednisolone was 46 milligrams per day which lasted for 3.81 months, on average. The follow-up period ranged between 1 and 60 months.
Table 1. Summary of the data provided for treatment groups

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Number of Studies</th>
<th>Total Number of Patients</th>
<th>Study Design</th>
<th>Follow-up (month)</th>
<th>Recurrence / Number of available data (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only corticosteroid</td>
<td>31</td>
<td>359</td>
<td>Case Report</td>
<td>14</td>
<td>1-60</td>
</tr>
<tr>
<td>Corticosteroid plus antibiotics</td>
<td>13</td>
<td>223</td>
<td>Cross-sectional</td>
<td>8</td>
<td>6-40</td>
</tr>
<tr>
<td>Corticosteroid plus immunosuppressant drugs</td>
<td>6</td>
<td>114</td>
<td>Clinical Trial</td>
<td>3</td>
<td>13-34</td>
</tr>
<tr>
<td>Corticosteroid plus surgery</td>
<td>12</td>
<td>228</td>
<td>Cohort</td>
<td>4</td>
<td>7-41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Case-Control</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

The exclusion criteria included insufficient detail about the recurrence of the disease, which resulted in the removal of 57 out of 289 patients.

Corticosteroid plus Antibiotics

Thirteen studies reported using corticosteroids and antibiotics as initial treatment. Case reports, cross-sectional and clinical trials were used in 8, 3, and 2 of these studies, respectively. The mean dosage of prednisolone was 51.25 milligrams per day. The follow-up period ranged from 6 to 40 months. Totally, 223 patients were included in this group. Of 181 cases for which sufficient details were provided, only one recurrence and 55 non-response cases were reported, and others had complete resolution during the follow-up period. Many drugs had been used as antibiotics, including Azithromycin, Amoxicillin, Amoxicillin and Cefadroxil, Dicloxacillin, Trimethoprim and sulfamethoxazole, Cloxacillin, Cloxacillin or Ciprofloxacin or Clindamycin, Amoxicillin or combined Amoxicillin and Clavulanic acid.

Corticosteroid plus Immunosuppressant Drugs

Out of the 58 selected studies, six had patients treated with a combination of corticosteroids and immunosuppressant drugs. Three of the studies were retrospective, and the remaining three were either case reports or case series. One hundred and fourteen patients were included in these studies, 73 of whom received a combination of prednisolone and an immunosuppressant. Prednisolone's mean dosage was 46.1 milligrams per day. After the exclusion of the missing data, the mean duration of treatment ranged from 4 to 24 months, and the meantime of follow-up was 13.83-34. The immunosuppressant combined with prednisolone was methotrexate in one study and azathioprine in three.

The other two studies administered both Azathioprine and Methotrexate in different treatment groups. Overall, 55 patients received prednisolone and methotrexate, 7 of whom had recurrences, and one had no response. Eighteen patients received prednisolone and azathioprine, 3 of whom had recurrences. The following side effects were only reported in 3 studies: severe skin acne, hair loss, hyperglycemia, hepatitis, temporary steroid-induced diabetes mellitus, cushingoid appearance, mood disturbances, and hyperprolactinemia.

Corticosteroid plus Surgery

Among the 58 studies, 12 studies had at least one treatment group treated with a combination of surgery and corticosteroids. A wide range of surgery methods were used, including wide local excision, partial mastectomy, and abscess drainage. In terms of study design, 5 studies were retrospective cross-sectional, 4 were case reports, 2 were case-control studies, and one was a cohort study. The mean prednisolone dosage was 40.6 milligrams per day. Overall, 443 patients were included, 228 of whom received a combination therapy of prednisolone and surgery. After excluding the missing data, the duration of treatment and follow-up ranged from 1 to 4 months and 7 to 41 months, respectively. Surgical interventions were abscess drainage, local excision, total excision, and partial mastectomy. Among the 228 patients that received a combination of surgery and corticosteroids, IGM recurred in 36 patients, and one patient had persistent disease.

Other Combinations

Some treatment groups did not fit into the prior treatment groups. The first category was those who used more complex or unpopular combinations, such as antibiotics plus surgery plus corticosteroids,
The second category was treatment groups that did not contain corticosteroids, only surgery, antibiotics plus surgery plus corticosteroids. The latter category was in the parent study containing other treatment groups with corticosteroids.

**DISCUSSION**

We reviewed the literature on the usage of corticosteroids in IGM treatment. Four main treatment modalities were identified, including only corticosteroid, corticosteroid plus antibiotics, corticosteroid plus surgery, and corticosteroid plus immunosuppressant drugs (sorted by frequency). The characteristics of the studies included and the categories identified have been reported in Tables 1 and 2.

The heterogeneity in the methodology of the published articles was an obstacle to determining the most effective treatment modality. Also, clinical trials and cohorts were scarce. Based on our analyses (Table 1), only 3 clinical trials were conducted on this topic, and none of them was randomized. In contrast, 84 percent of the published articles were case reports and series or cross-sectional in terms of the methods of the study. So, the shortage of evidence in many of the studies is the reason why the effectiveness of corticosteroids on IGM has been controversial among researchers for a long time. Even the large number of conducted studies, including two systematic reviews and meta-analyses, did not provide ample evidence to resolve this controversy. This might be due to the heterogeneity and also the low number of randomized clinical trials among previous surveys. This is compatible with the findings of Lei et al. (2017), in which no prospective studies were found. However, Godazande et al. (2021) claimed that they had included 12 clinical trials based on the explained methodology, but we did not qualify most of them as clinical trials in our study, and were not convinced of the reliability of the results reported in their meta-analysis. Our findings emphasize a need for performing double-blind, randomized surveys with a control or placebo group to draw a more definite conclusion as to the effect of corticosteroids on IGM treatment.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of the articles</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type (n = 58)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial</td>
<td>3</td>
<td>5.17</td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>5.17</td>
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<tr>
<td>Cross-sectional</td>
<td>20</td>
<td>34.48</td>
</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>5.17</td>
</tr>
<tr>
<td>Case series/reports</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td><strong>Year of publication (n = 58)</strong></td>
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<td></td>
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<tr>
<td>Before 2000</td>
<td>3</td>
<td>5.17</td>
</tr>
<tr>
<td>2000-2010</td>
<td>15</td>
<td>25.86</td>
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<tr>
<td>2010-2015</td>
<td>21</td>
<td>36.20</td>
</tr>
<tr>
<td>After 2015</td>
<td>19</td>
<td>32.75</td>
</tr>
<tr>
<td><strong>Treatment category (n = 115)</strong></td>
<td></td>
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<tr>
<td>Only corticosteroid</td>
<td>32</td>
<td>27.8</td>
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<tr>
<td>Corticosteroid plus antibiotics</td>
<td>13</td>
<td>11.3</td>
</tr>
<tr>
<td>Corticosteroid plus immunosuppressant drugs</td>
<td>9</td>
<td>7.8</td>
</tr>
<tr>
<td>Corticosteroid plus surgery</td>
<td>13</td>
<td>11.3</td>
</tr>
<tr>
<td>Other combinations</td>
<td>48</td>
<td>41.8</td>
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<td><strong>Dosage of corticosteroid (n = 58)</strong></td>
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<td></td>
</tr>
<tr>
<td>Clearly marked</td>
<td>56</td>
<td>96.6</td>
</tr>
<tr>
<td>Partially reported</td>
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<td>0</td>
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<tr>
<td>Not reported</td>
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<td>3.4</td>
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<tr>
<td><strong>Duration of corticotherapy (n = 58)</strong></td>
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</tr>
<tr>
<td>Clearly marked</td>
<td>56</td>
<td>96.6</td>
</tr>
<tr>
<td>Partially reported</td>
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<td>0</td>
</tr>
<tr>
<td>Not reported</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Follow-up data (n = 58)</strong></td>
<td></td>
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</tr>
<tr>
<td>Clearly marked</td>
<td>40</td>
<td>69.0</td>
</tr>
<tr>
<td>Partially reported</td>
<td>17</td>
<td>29.3</td>
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<tr>
<td>Not reported</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Recurrence/attacks of disease (n = 58)</strong></td>
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<tr>
<td>Clearly mentioned</td>
<td>53</td>
<td>91.4</td>
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<tr>
<td>Partially reported</td>
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<td>6.9</td>
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<tr>
<td>Not clear</td>
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<td>1.7</td>
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<tr>
<td><strong>Corticosteroids side effects (n = 58)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly marked</td>
<td>11</td>
<td>19.0</td>
</tr>
<tr>
<td>Not clear</td>
<td>47</td>
<td>81.0</td>
</tr>
</tbody>
</table>

Regarding the follow-up data in the studies evaluated in the present article, even the published retrospective studies were not homogenous enough for drawing a conclusion. A few surveys followed a...
specific trend in the patient evaluation, classification of the severity of the disease, diagnostics and treatment, and the reporting of the outcomes. For example, few papers described the severity of the disease, and the criteria for prescription of different treatments. Furthermore, the definition of follow-up in most of the published articles (whether at the beginning of treatment or after remission) was not identical, and those studies that reported the follow-up (69% of the studies included) used different methods for reporting the time (i.e., range or mean).

It is clear that to be able to make a conclusion regarding the effect of any given medication on a certain disease, we need detailed information about the treatment, e.g., the route of treatment administration, the dosage of the medication, and concurrent use of the medication with the other treatments. Even for reporting the dose of the administered corticosteroids, different units have been used, such as mg/kg and mg. This issue has also been addressed in the review by Lei et al. (2017), who found that seven of the fifteen studies reviewed did not report a recurrence rate, and two did not report a complete remission rate. This reporting heterogeneity can also be seen in inclusion criteria, disease severity, and treatment side effects. This consideration makes it impossible to conduct a reliable systematic review and meta-analysis on this topic.

In the current study, we have presented the therapeutic measures in the published articles in four categories. The highest number of patients belonged to the groups treated only with corticosteroids, followed by a combination of corticosteroids and surgery, antibiotics, and immunosuppressant drugs, respectively. In comparison, a review of 70 studies by Martinez et al. found that the most frequent treatment for IGM in developed countries was corticosteroid therapy, followed by surgery as the second most common treatment. They also found that the most frequent treatment in non-developed countries was antibiotic therapy.

Based on the studies included in this review, complete remission was reported inconsistently. However, not taking the missing data into account, the recurrence rate was 19.7% for the only-corticosteroids group and 0.5%, 13.7%, and 15.8% for the combination of corticosteroids-antibiotics, corticosteroids-surgery, and corticosteroids-immunosuppressives, respectively. This finding is not reliable enough, considering that the dosage of the corticosteroids, the duration of treatment, the sequence of each treatment in combined treatments, and the severity of the disease before starting the treatment were not consistent in these studies.

In comparison, the systematic review by Lei et al. evaluated the complete remission (CR) and recurrence rates in fifteen studies. They found a recurrence rate of 20.9% in patients treated only with oral corticosteroids, 4% in patients treated with surgical management and oral corticosteroids, and 9.2% in patients managed only by observation. They reviewed three studies administering a combination of methotrexate and corticosteroids, only one of which reported disease recurrence and no recurrences. They also reported CR rates in the groups and discussed the lack of an agreed-upon definition of CR. Also, in the studies included in our report, CR was not defined and reported consistently as we have emphasized.

When deciding on the type of treatment for IGM and the effectiveness of the treatment, side effects should be considered. IGM is a chronic and recurrent disease, and the patients may need long courses or multiple high-doses of corticosteroid treatment. It has been shown that long-term use of systemic corticosteroids can have adverse effects such as weight gain, cataracts, acne, sleep disturbance, fractures, and skin bruising. Also, short-term use of corticosteroids may lead to an increased risk of adverse events including, but not limited to, sepsis, fracture, and venous thromboembolism. Therefore, there is a need to assess the benefits and disadvantages of corticosteroids to comment on their role in the treatment of IGM in the clinical setting. In the articles included in this study, there was inconsistency in reporting the duration of use, corticosteroid dosage and type, and the intensity of acute and chronic adverse effects of corticosteroids. Of the 58 studies, 96.6% reported the duration of treatment, 96.6% reported the corticosteroids dosage, and only 19% reported the adverse events. Some side effects of steroids may appear long-term. Considering the fact that in this study only 69% of the citations clearly reported the time of follow-up ranging from 1 to 60 months, some of the long-term side effects could not be evaluated. Thus, further studies are needed to weigh the side effects of corticosteroids against their effectiveness.

CONCLUSION

The findings of our study suggest that the use of corticosteroids, alone or in combination with other therapies, can be effective in the treatment of IGM. However, considering the heterogeneity of studies in reporting the severity of disease, administered treatments, outcome of treatment, side effects, and follow-up, it is hard to draw a decisive conclusion on this matter. This study could not provide solid evidence for using corticosteroids as the first step in managing idiopathic granulomatous mastitis.
Nevertheless, it confirms the need for further studies, emphasizing the homogenization of reports on the severity and symptoms of IGM, type, the dosage of treatment, and the effects of the treatment on the short-term and long-term course of the disease. In this regard, preparing a questionnaire to help homogenize future reports on IGM is highly recommended.

CONFLICTS OF INTEREST
All of the authors declare that they have no conflicts of interest.

REFERENCES

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Corticosteroids in IGM


