

# *Mycophenolate mofetil in primary Sjögren's syndrome: a treatment option for agranulocytosis*

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## ABSTRACT

The Sjögren's syndrome (SS) is an autoimmune disease characterized by a lymphocytic infiltration of salivary and lacrimal glands. Hematological manifestations of primary SS (pSS) usually consist of mild anemia, thrombocytopenia, moderate neutropenia, and lymphopenia. Agranulocytosis is rarely reported and usually responds to immunosuppression. We report the case of a pSS patient who presented with refractory agranulocytosis. Bone marrow biopsy disclosed a hypocellular bone marrow with normal maturation of the granulocytic series. The patient was successively treated with high-dose prednisone, granulocyte-macrophage colony stimulation factor, and cyclosporine, with no hematological response. Mycophenolate mofetil (MMF) was initiated and after two months there was a rise on the white blood cell count. After one year of follow-up, she had neither further neutropenia episodes, nor infectious complications. We conclude that, in pSS refractory agranulocytosis, MMF can be an effective and well-tolerated treatment option.

**Keywords:** neutropenia, agranulocytosis, treatment outcome, immunosuppressive agents, Sjögren's syndrome.

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## INTRODUCTION

The Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of salivary and lachrymal glands leading to a progressive destruction of these glands.<sup>1</sup> It can occur as a localized syndrome primarily causing the sicca syndrome (mouth and eye dryness) or as a systemic disease affecting multiple organs. Also, the disease occurs as a primary or secondary disorder. As a primary disorder, a patient with no known connective tissue disease develops the classical sicca symptoms.

Hematological manifestations of primary SS (pSS) usually consist of mild anemia and thrombocytopenia, as well

as moderate neutropenia and lymphopenia.<sup>1</sup> Unexplained agranulocytosis has been rarely reported in patients with pSS.<sup>2-4</sup> Bone marrow neutrophil production may be affected, or neutrophils may be destroyed in the circulation, by both humoral and cellular immune-mediated mechanisms. The pSS associated agranulocytosis usually responds to steroids used alone or with immunosuppressive drugs.<sup>2,4,5</sup> By contrast, in one study, steroids alone were ineffective and an association with methotrexate resulted in only a partial and transient response.<sup>6</sup>

Here, we describe the case of a pSS patient who developed refractory agranulocytosis and was successfully treated with mycophenolate mofetil (MMF).

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## CASE REPORT

A 69 year-old woman with chronic xerostomia and xerophthalmia was admitted to our hospital because of a community-acquired pneumonia. She previously had had pancytopenia and had already been submitted to a bone marrow smear and biopsy in another medical center, which resulted normal. On admission, blood tests showed hemoglobin 11.4 g/dL, hematocrit 34.3%, and platelets 317,000. The white blood cell count was 2,800, with 14% neutrophils, giving a neutrophil count of 392. Erythrocyte sedimentation rate was 19 mm/h, C-reactive protein level was 2 mg/L, and creatinine level was 1 mg/L. Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia. Rheumatoid factor and antinuclear antibody test (1:320) were both positive, but anti-SSA/SSB were negative. An ophthalmologic evaluation confirmed keratoconjunctivitis sicca and a corneal ulcer. Bone marrow biopsy disclosed a hypocellular marrow with normal maturation of the granulocytic series and a normal immunophenotyping.

The patient was initially treated with intravenous ceftazidime 1 g every 8 hours, prednisone 60 mg/day and granulocyte-macrophage colony stimulation factor (G-CSF). After clinical stabilization she was discharged for our outpatient clinic but was readmitted three other times with agranulocytosis, being again treated with high dose corticosteroids and G-CSF. Despite of that, she still presented with a white blood cell count of 5,130 and 0 neutrophils. The treatment with cyclosporine up to 100 mg twice a day for eight months resulted in no hematological response (3,180 white blood cells and 60 neutrophils). We finally decided to initiate MMF treatment 2 g/day, and after two months the white blood cell count was of 3,510 with 2,200 neutrophils. Prednisone dose was progressively tapered to 2.5 mg/day. After eight months her white blood cell count was 4,620, with 2,543 neutrophils. After one year of follow-up, although the patient did not improve ocular or oral dryness, she had no other neutropenia episodes or infectious complications.

Patient's informed consent was obtained according to the declaration of Helsinki and this work was approved by

the Ethics Committee on Human Being Research of the Universidade Federal de Santa Catarina, Brazil.

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## DISCUSSION

Mycophenolic acid (MPA) is a selective inhibitor of inosine monophosphate dehydrogenase which leads to inhibition of the *de novo* pathway of nucleotide synthesis. The antiproliferative effect of MPA mainly affects activated T and B lymphocytes, because the proliferation of these cells is critically dependent on the *de novo* purine synthesis, compared with other eukaryotic cells.<sup>7</sup> Since these lymphocytes have been suggested to play a pivotal role in the immunopathogenesis of pSS,<sup>8</sup> MPA might be a promising agent in the treatment of this syndrome.

Investigations about the efficacy and safety of MMF in pSS have still to be performed in larger numbers of patients. However, MMF had been used as maintenance therapy after treatment with rituximab (anti-CD20 antibody)<sup>9</sup> and in the treatment of vasculitis associated pSS.<sup>10</sup> These observations and the immunosuppressive effect of MPA in other autoimmune diseases led Willeke *et al.*<sup>10</sup> to evaluate (in an open label controlled pilot trial) the efficacy and safety of MMF treatment in patients with pSS refractory to other immunosuppressive agents. In general, MMF treatment resulted in subjective improvement of ocular dryness on a visual analogue scale and a reduced demand for artificial tear supplementation. However, no significant alterations of objective parameters for dryness of eyes and mouth were observed. In addition, the treatment with MMF resulted in significant reduction of hypergammaglobulinemia and rheumatoid factors as well as an increase of complement levels and leukocytes/neutrophils count, suggesting that MMF also might be effective in treating pSS-associated leukopenia.

In summary, agranulocytosis is a rare but well established association with pSS and it usually responds to steroids used alone or in association with immunosuppressive drugs. However, in one study and in our patient, steroids alone were ineffective, and the association with immunosuppressors resulted in only a partial and transient response. In those patients, MMF can be an effective option for treatment.

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