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Original Article / Özgün Araştırma

Efficacy of mycophenolate mofetil treatment in patients with immune thrombocytopenia who have received at least one series of treatment: a single-center study

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Abstract

Background: The objective of this study was to evaluate the efficacy of mycophenolate mofetil (MMF) as a second- or third-line treatment for chronic immune thrombocytopenia (ITP).

Methods: A cohort of 13 patients with chronic ITP, who had previously been treated with eltrombopag, corticosteroids, or both, without achieving an effective response, was administered mycophenolate mofetil at a daily dosage of 1000 mg. Platelet counts were monitored at the fourth and twelfth weeks of treatment.

Results: In our study, 13 patients were included, consisting of 4 females (30.8%) and 9 males (69.2%). At the 12-week mark following the initiation of MMF therapy, three out of 13 patients achieved a complete response, three out of 13 patients achieved a partial response, and seven patients showed no response. (Fig.1). At the time of transitioning to Mycophenolate Mofetil (MMF), all patients had a platelet count below 30 × 10^9/L. Approximately 40% of patients experienced an increase in platelet counts to levels above 30 × 10^9/L.

Conclusions: Mycophenolate mofetil may be considered a potential treatment option for patients with chronic ITP who are refractory to first- and second-line therapies.

Keywords: Mycophenolate mofetil, Thrombocytopenia, Refractory

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En az bir seri tedavi almış immun trombositopeni tanılı hastalarda mikofenolat mofetil tedavisinin etkinliği: tek merkez çalışması

Öz

Amaç: Bu çalışmanın amacı, kronik immün trombositopeni (İTP) tedavisinde ikinci veya üçüncü basamak tedavi olarak mikofenolat mofetilin (MMF) etkinliğini değerlendirmektir.

Yöntemler: Daha önce eltrombopag, kortikosteroidler veya her ikisiyle tedavi edilmiş ve etkili bir yanıt alınamamış kronik İTP'li 13 hastadan oluşan bir kohorta, günlük 1000 mg mikofenolat mofetil uygulandı. Trombosit sayıları, tedavinin dördüncü ve on ikinci haftalarında izlendi.

Bulgular: Çalışmamıza 4 kadın (%30,8) ve 9 erkek (%69,2) olmak üzere toplam 13 hasta dahil edildi. MMF tedavisinin başlamasından sonraki 12. haftada, 13 hastanın 3'ünde tam yanıt, 13 hastanın 3'ünde yanıt ve 7 hastada yanıt alınamamıştır. Mikofenolat Mofetil'e (MMF) geçiş sırasında tüm hastaların trombosit sayısı 30 × 10^9/L'nin altındaydı. Hastaların yaklaşık %40'ında trombosit sayılarında 30 × 10^9/L'nin üzerine çıkan bir artış görüldü.

Sonuç: Mikofenolat mofetil, birinci ve ikinci basamak tedavilere dirençli kronik İTP'li hastalar için potansiyel bir tedavi seçeneği olarak düşünülebilir.

Anahtar kelimeler: Mikofenolat mofetil, Trombositopeni, Dirençli.

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune condition marked by severe reduction in platelets, often with varying bleeding symptoms. Despite low platelet counts, serious hemorrhages are uncommon[1]. Treatment decisions are made based on an individual's bleeding risk, considering factors like platelet count, bleeding history, comorbidities, medications, previous treatment responses, and lifestyle aspects such as fatigue. Although the exact cause of ITP remains unclear, it is believed that peripheral platelet destruction and impaired bone marrow production are key processes [2-4]. Primary immune thrombocytopenia is characterized by isolated thrombocytopenia (platelet count <100 × 10^9/L) without any known cause[5].

The pathogenesis of ITP is complex, involving peripheral platelet destruction occurring in the blood, spleen, and liver, combined with insufficient bone marrow production due to autoimmune attacks on megakaryocytes and low thrombopoietin (TPO) levels2.

The standard approach for ITP starts with corticosteroids and intravenous immunoglobulin (IVIG) as first-line treatments. If needed, second-line options include thrombopoietin receptor agonists (eltrombopag or romiplostim), rituximab, and splenectomy[6]. These treatments vary; some aim to induce a lasting response (such as rituximab or splenectomy), while others require ongoing use (like immunosuppressants or thrombopoietin receptor agonists). Consequently, treatment choices are tailored to each patient's tolerance of severe thrombocytopenia and potential side effects. Most guidelines recommend starting therapy when the platelet count drops below 30 × 10^9/L, due to the increased risk of bleeding that warrants preventive action[7].

Mycophenolate mofetil (MMF), also known as Celof mycophenolic acid (MPA), inhibits inosine-5'-monophosphate dehydrogenase. MPA mainly depletes guanosine nucleotides in T and B lymphocytes, reducing their proliferation and thereby suppressing cell-mediated immune responses and antibody production[8]. MMF generally exhibits a tolerable side effect profile and is used in various

autoimmune disorders, including preventing acute rejection in renal or cardiac transplants[9]. Additionally, MMF serves as a second-line treatment for ITP. However, because refractory ITP is rare, there are few comparative trials of all second-line options, making it difficult to recommend one agent over another.

METHODS

Between 2019 and 2023, the haematology clinic at Dicle University documented cases of severe ITP treated with MMF. This service review anonymously identified patients receiving MMF as part of routine treatment. Included were patients with primary ITP who required second-line therapies beyond steroids or IVIg. Bleeding symptoms ranged from oral mucosal bleeding, petechiae, and rectal bleeding to intracerebral hemorrhage. Data collected included patient demographics, comorbidities, diagnosis dates, and previous treatments. Key endpoints were treatment response, response duration, MMF dose, concurrent therapies like steroids, and adverse effects. The study was conducted under the decision number 301, dated 22.04.2021, from the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

Response Criteria/Definitions

Response to ITP therapy was defined as the ability to maintain a platelet count sufficient to prevent clinically significant bleeding. Definitions of response included:

1. Complete Response (CR): Platelet count ≥ 100 × 10^9/L.

2. Response (R): Platelet count ≥ 30 × 10^9/L with at least a two-fold increase from baseline.

3. No Response: Platelet count < 30 × 10^9/L or less than a two-fold increase from baseline, with ongoing bleeding symptoms.

Patients

Thirteen patients with primary ITP were followed over four years: Nine males and four females. Six patients had comorbidities such as diabetes mellitus and hypertension, and all had received multiple treatment lines, ranging from methylprednisolone to eltrombopag. Initial platelet counts before starting MMF were below 25 × 10^9/L; eight patients had counts below 15 × 10^9/L. MMF was initiated at 1 gram/day (divided into two doses), with a maximum dosage of 2 grams/day.

Response was assessed at the twelfth week of treatment, revealing three patients with a complete response and four patients with a response, while six patients showed no response (figure 1).

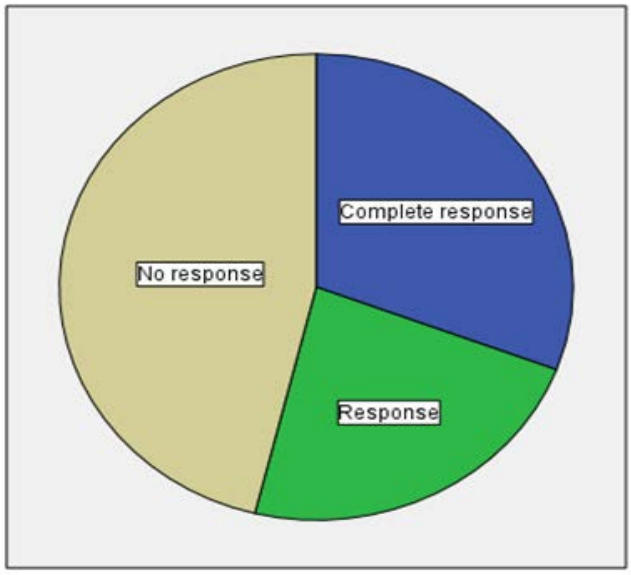

Figure 1. No response Response Complete response

RESULTS

In our study, 13 patients were included, consisting of 4 females (30.8%) and 9 males (69.2%). Six patients (46.2%) had comorbidities, primarily hypertension and diabetes mellitus. All patients were diagnosed with primary Immune Thrombocytopenia (ITP)

and had undergone multiple treatment regimens, excluding splenectomy.

At the 12-week mark following the initiation of MMF therapy, 3 out of 13 patients (23.1%) achieved a complete response, 3 out of 13 (23.1%) had a response, and 7 out of 13 (53.8%) showed no response (Fig.1). At the time of transitioning to Mycophenolate Mofetil (MMF), all patients had a platelet count below 30 × 10^9/L (Fig. 2).

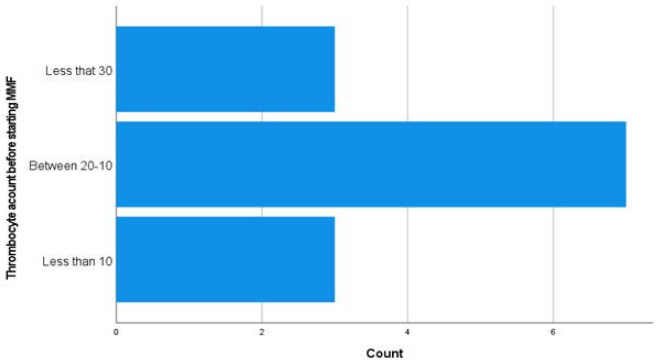

Figure 2. Thrombocytes account before starting MMF

Notably, among those who achieved a complete response (2 males, 1 female), none had comorbidities. In the partial response group (2 males, 1 female), only one patient had hypertension as a comorbidity. The mean age of all patients was 43.8 years, with a range of 22 to 76 years. Patients who achieved a complete response were younger, aged 34, 36, and 22 years, respectively. The age range of the partial response group was broader, spanning from 41 to 66 years. No side effects were observed in our patients regarding MMF.

It was observed that patients with a complete response had no comorbidities. Additionally, when we only considered patients who achieved complete and partial responses, the ratio was 5:1 in favor of men.

DISCUSSION

The primary treatment for immune thrombocytopenia (ITP) typically begins with corticosteroids, which serve as the initial therapy aimed at increasing platelet counts by suppressing the immune-mediated destruction of platelets. While splenectomy was historically a common next step for persistent cases, the advent of newer therapeutic agents has reduced the necessity for surgical interventions. If corticosteroids are insufficient, second-line treatments vary depending on individual patient characteristics and response. Options may include intravenous immunoglobulin (IVIg) or thrombopoietin receptor agonists (TPO-RAs) such as eltrombopag or romiplostim. In cases of refractory ITP, more intensive therapies like anti-CD20 monoclonal antibodies (e.g., rituximab) or certain chemotherapy regimens may be employed [10].

The pathophysiology of ITP is complex, involving multiple mechanisms of platelet destruction both peripherally and centrally. These mechanisms include autoantibody-mediated platelet clearance, complement activation, cytotoxic T-cell activity, and impaired platelet production due to megakaryocyte dysfunction. This complex interplay results in significant variability in treatment responses among patients[11].

Mycophenolate mofetil (MMF) is an immunosuppressant with broad application, particularly in organ transplantation, but it has also been studied in ITP treatment. MMF works primarily by inhibiting inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in the de novo synthesis of guanine nucleotides. This inhibition is selective for lymphocytes, significantly reducing both their activation and proliferation. Additionally, MMF suppresses B-cell antibody production, thereby affecting the overall immune response. The active form, mycophenolic acid (MPA), targets IMPDH and impacts RNA and DNA synthesis, further diminishing lymphocyte proliferation[12].

Many studies have focused on the role of Mycophenolate Mofetil (MMF) in the treatment of immune thrombocytopenia (ITP). A systematic meta-analysis of MMF use in ITP patients reported a 63% total response rate (combining both complete and partial

responses), alongside a favourable safety profile for MMF[13]. Another study involving 20 refractory cases of ITP revealed that administering MMF at doses ranging from 1 gram/day to a maximum of 2 grams/day resulted in a high response rate, with 80% overall response and 45% achieving complete response[14]. Further research assessed MMF's potential as a first-line treatment, either alone or in combination with steroids, and concluded that ITP patients treated with a combination of steroids and MMF experienced lower recurrence rates and a higher remission profile[15]. Additionally, MMF has been considered as a steroid-sparing agent, particularly in severe cases of ITP[4]. The response rate we obtained in our study was found to be lower compared to the studies we mentioned. Possible reasons for this could be the smaller number of patients.

Ethical Approval: The study was conducted under the decision number 301, dated 22.04.2021, from the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

Conflict of Interest: The authors declared no conflicts of interest.

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