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Therapeutic efficacy and clinical effectiveness of mycophenolate mofetil and dexamethasone for immune thrombocytopenia: A retrospective observational study

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Abstract:

BACKGROUND: Immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disorder, where autoreactive T-cells and/or autoantibodies destroy platelets and megakaryocytes in the spleen and bone marrow, respectively. To the best of our knowledge, this is the largest cohort of cases wherein patients were treated with novel combination therapy of a corticosteroid with an adjunct immunosuppressive agent for the treatment of ITP in adults. In cohort of 23 patients, 11 patients have no response and 12 patients have shown partial to complete response (CR) to the treatment. The primary aim of the present study was to explore the safety and efficacy of combination therapy in chronic ITP along by evaluating the toxicity associated with prolonged steroid exposure. The secondary aim was to compare the cost benefit with other available modalities for chronic ITP treatment.

MATERIALS AND METHODS: A retrospective observational study was carried out by collecting data from electronic medical records of all the ITP patients treated at HCG Manavata Cancer Centre, India, between May 1, 2019, and April 30, 2020. Inclusion and exclusion criteria were strictly followed for data collection and analysis.

RESULTS: Twelve (52%) of the 23 patients have shown response to the combinational therapy; 5 (22%) patients achieved a partial response (PR) and 7 (30%) achieved a CR. In the PR group, 3 patients developed thrombocytopenia and 1 switched to thrombopoietin receptor agonists, whereas in 7 CR patients, 6 have maintained it until end and 1 patient was switched to maintenance therapy.

CONCLUSION: A combination of immunosuppressant and corticosteroid on ITP patients appeared to be effective, tolerable, with minimal adverse side effects, and an economical alternative. Therefore, this novel combination therapy may be an excellent alternative for the treatment of patients with ITP in clinical settings.

Keywords:

Autoimmune disease, dexamethasone, immune thrombocytopenia, mycophenolate mofetil

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Introduction

Immune thrombocytopenia (ITP) is a common hematological condition that is characterized by low platelet count. ITP could be present in a primary or secondary form. In the primary form, it is characterized by the presence of isolated thrombocytopenia with a platelet count of $<100 \times 10^9$/L compared to normal platelet count in healthy individuals ranging from 150×10^9/L to 400×10^9/L.[1] In the secondary form, ITP may develop in relation

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to an existing disorder, specifically an infectious or immune ailment. ITP prevalence is observed in all age groups, genders, and races without any disparities.[2]

Destruction and decrease in platelet count in the body contributing to the ITP are generally happened by immune-mediated destruction or decreased production. In such cases, symptoms differ largely from bleeding gums, nosebleeds, petechiae, rectal bleeding to intracerebral hemorrhages depending on the severity of the disease.[1,2]

Due to the limited knowledge and scientifically backed data, previously, it was termed as "idiopathic thrombocytopenic purpura." However, with the advancement of technology and research in ITP management, standardized treatment protocols were determined. With these recent scientific and research developments, the International ITP Working Group (IWGITP) has removed the term acute/idiopathic and renamed the disease as "ITP." Further classification of ITP was done and recommended the new terminologies such as newly diagnosed ITP (up to 3 months after initial diagnosis), persistent ITP (symptoms lasting between 3 and 12 months), and chronic ITP (symptoms lasting >12 months).[3]

Over that, IWGITP has also recommended tailored treatment principles and line of therapies to the patients who are highly dependent on the platelet count and severity. In such exceptional cases of severe ITP, steroids were used as a first-line therapy, whereas intravenous immunoglobulin (IVIG) was used as a reserve in patients with severe bleeding complications.[4-6] Even though IVIG and steroids were observed to be safe, efficacious with excellent response rates. Still, the relapses are found to be quite evident. The relapses are found to be quite evident.[4,5] As per the current evidence, rituximab was showing a good response rate of 40% as a second-line therapy for the 1st year. However, in 5-year follow-up studies, the response rate was observed to be reduced to 20%.[7-9]

Splenectomy is another ideal approach in patients with chronic ITP as a part of curative treatment with a long-term response rate of 66%–88%.[10,11] Splenectomy was also having a relatively poor relapse rate of 15%, which is commendable.[10,11] However, the major limiting factor with this procedure is bleeding associated with the surgery and the risk of surgical complications to be followed.

Another treatment option is the usage of thrombopoietin receptor agonists (TPO-RAs), which are known for their excellent response rate of 80%.[12] However, they are required to take for prolonged periods of time due to their suspensive effect.[8] The long-term response rate of TPO-RA was observed to be in the range of 15%–30%, whereas in case of multirefractory patients, the use of immunosuppressive drugs such as cyclophosphamide, cyclosporine, azathioprine, and mycophenolate mofetil (MMF) can be considered alone or in combination.[13] Among them, MMF was widely used and its efficacy in ITP was first reported in the early 90s. There have been multiple clinical studies that have confirmed the potential benefits of MMF as a second-line therapy in patients with ITP with a response rate of 40%–80%.[4,14-16]

With advancement in novel treatments, financial implications related to them have also become a major limiting factor. Very few studies have associated with the management of ITP and the cost associated with it. To give a clear insight, in the present study, we are assessing the safety and efficacy of combination therapy (MMF with dexamethasone [DEXA]), along by evaluating the cost associated with the treatment and hospitalization.

Materials and Methods

This retrospective observational study was conducted at HCG Manavata Cancer Centre, India. The study was initiated after receiving all the necessary approvals from the Institutional Ethics Committee (Protocol – MMDITP-2020). Medical records of all the patients treated for severe ITP using MMF and DEXA from May 1, 2019, to April 30, 2020, were collected and analyzed. Patients with primary or secondary ITP and who are under the first line of therapy were excluded from the analysis. Patients were evaluated and investigated as per the American Society of Hematology 2011 guidelines for ITP. Primary investigations such as peripheral smear examination, human immunodeficiency virus, hepatitis B surface antigen, anti-hepatitis C virus, thyroid function test, and antinuclear antibody workup were done in all the patients. Among 23 patients, 15 patients had baseline bone marrow examination and 8 patients underwent bone marrow aspiration before initiating the therapy. All the bone marrow-aspirated slides were examined and reviewed by a hematopathologist.

Inclusion criteria include patients under the second line of therapy with moderate-to-severe symptoms. A total of 23 patients (14 males and 9 females) were identified with a median age of 37 years (age range: 18–92 years). The median duration of treatment and follow-up period was found to be 26 weeks (16–43 weeks) and 12 months (2–40 months), respectively. All the patients were continuously monitored for their initial response, duration of response, and side effects related to the treatment.

Results

Before inclusion in the present study, patients were treated with various drug therapies, as summarized in Table 1, with a median number of treatments ranging from 1 (n = 7) to 7 (n = 2). The time interval between the initial diagnosis and treatment initiation was observed to be around 25 months (range: 1–184 months). In 23 patients, 15 patients had primary ITP and 8 had secondary ITP, respectively. Among 23 patients, 8 patients were also associated with autoimmune disorders. All the patients included in this study were due to relapse and were initiated on combinational therapy [MMF and DEXA, Table 2] for better treatment outcomes. Treatment options, clinical responses, and the overall financial constraints involved during the treatment are also presented in Table 3. Based on their response to planned treatment and outcome, as shown in Table 4, patients were classified into three groups as complete response (CR), partial response (PR), and no response to treatment. As shown in Figure 1, among 23 patients, 7 patients have shown CR, 5 patients PR, and 11 patients no response at all. To maintain safe platelet levels throughout the treatment period, patient's platelet count was continuously monitored from day 1 (week 0) to the last day of the treatment (~12 weeks).

Table 1: Treatments used before mycophenolate mofetil and dexamethasone were documented

Drug name	Number of patients (percentage of total patient cohort), *n* (%)
Immunoglobulin	15 (65)
Steroids	14 (60)
Rituximab	2 (8)
Splenectomy	2 (8)
Azathioprine	4 (17)
Anti-D	2 (8)
Eltrombopag	2 (8)

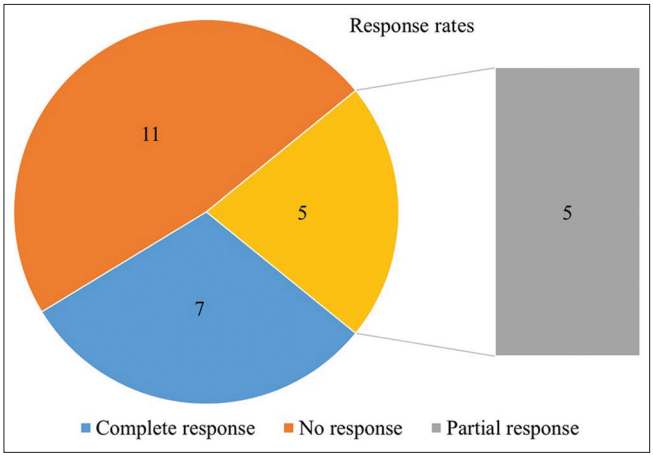

Figure 1: Response rate of mycophenolate mofetil and dexamethasone in study cohort

Table 2: Response to combination therapy of mycophenolate mofetil and dexamethasone therapies

Patients (*n*=23)	MMF (g/day)	DEXA (mg) (day 1-day 4) 1st and 3rd week of the month	Duration of combination therapy (weeks)	Platelets (week 0) 109/l	Platelets (week 12) 109/l	Response
1	1.0	40	16	20	250	CR
2	1.0	40	17	11	11	NR
3	1.0	40	24	15	3	NR
4	1.5	40	16	30	300	CR
5	1.5	40	19	3	5	NR
6	0.75	40	20	4	45	PR
7	1.0	40	24	5	200	CR
8	1.0	40	26	9	9	NR
9	1.0	40	28	11	10	NR
10	1.5	40	29	15	245	CR
11	1.0	40	32	21	59	PR
12	0.5	40	26	22	11	NR
13	1.0	40	17	15	10	NR
14	1.5	40	19	21	145	CR
15	1.0	40	28	3	15	NR
16	1.0	40	22	9	20	NR
17	1.0	40	29	5	30	PR
18	1.0	40	43	11	123	CR
19	1.5	40	26	15	25	NR
20	1.0	40	33	14	124	CR
21	1.0	40	27	18	45	PR
22	1.5	40	29	19	20	NR
23	1.0	40	43	25	40	PR

NR=No response, PR=Partial response, CR=Complete response, MMF=Mycophenolate mofetil, DEXA=Dexamethasone

Table 3: Treatment options, clinical responses, and financial constraints involved in the treatment of patients with immune thrombocytopenia

Patient	MMF (g/day)	DEXA (mg)	Duration of treatment combination (in weeks)	Platelets (week 0) 109/l	Platelets (week 12) 109/l	Response rate	Clinical response and control of bleeding	Adverse events observed	Length of hospital stay (in days)	Treatment cost (in INR)	Hospitalization cost (in INR)	Commentary with respect to patient treatment	Initial response/ peak response (onset of action and peak effect/ efficacy) (in days)
1	1.0	40	16	20	250	CR	Yes	No	Nil	15,000/-	2000/-	FC	25
2	1.0	40	17	11	11	NR	Yes	No	Nil	15,000/-	2000/-	Clinical control	NR
3	1.0	40	24	15	3	NR	No	Hyperglycemia	5	15,000/-	12,500/-	Response to TPO	NR
4	1.5	40	16	30	300	CR	Yes	Gastritis	Nil	15,000/-	2000/-	Gastritis improved with PPI	35
5	1.5	40	19	3	5	NR	No	No	8	15,000/-	15,000/-	Lost to follow up	NR
6	0.750	40	20	4	45	PR	Yes	No	Nil	15,000/-	2500/-	FU	40
7	1.0	40	24	5	200	CR	Yes	No	Nil	15,000/-	2000/-	FU	31
8	1.0	40	26	9	9	NR	Yes	Weight gain	Nil	15,000/-	2000/-	FU	NR
9	1.0	40	28	11	10	NR	No	No	15	15,000/-	24,000/-	FC	NR
10	1.5	40	29	15	245	CR	Yes	No	Nil	15,000/-	2000/-	Could undergo surgery of hernia	24
11	1.0	40	32	21	59	PR	Yes	GI trouble	Nil	15,000/-	2000/-	FU	36
12	0.5	40	26	22	11	NR	No	No	11	15,000/-	15,000/-	Response to TPO	NR
13	1.0	40	17	15	10	NR	Yes	No	Nil	15,000/-	2000/-	FU	NR
14	1.5	40	19	21	145	CR	Yes	No	Nil	15,000/-	2000/-	FU	34
15	1.0	40	28	3	15	NR	No	No	5	15,000/-	7000/-	LTFU	NR
16	1.0	40	22	9	20	NR	Yes	No	Nil	15,000/-	5000/-	LTFU	NR
17	1.0	40	29	5	30	PR	Yes	No	Nil	15,000/-	2000/-	FU	55
18	1.0	40	43	11	123	CR	Yes	Dyspepsia	Nil	15,000/-	3000/-	Could participate in sports activity	34
19	1.5	40	26	15	25	NR	Yes	No	Nil	15,000/-	2500/-	FU	NR
20	1.0	40	33	14	124	CR	Yes	No	Nil	15,000/-	3000/-	FU	33
21	1.0	40	27	18	45	PR	Yes	No	Nil	15,000/-	3300/-	Off treatment	23
22	1.5	40	29	19	20	NR	No	No	11	15,000/-	19,000/-	FU	NR
23	1.0	40	43	25	40	PR	Yes	No	Nil	15,000/-	3000/-	FU	68

Various tablets used and their price range (In INR) - Decmax (GLS) (INR 34); Fenograf (Torrent) (INR 809); Mycept (Panacea) (INR 665); Cellcept (Roche) (INR 555); Revolade (Novartis) (INR 42000). NR=No response, PR=Partial response, CR=Complete response, FC=Financial constraints, FU=Follow-up, PPI=Proton-pump inhibitors, TPO=Thrombopoietin receptor agonists, LTFU=Lost to follow-up, INR=International normalized ratio

Table 4: Patients response to the treatment

Response	Number of patients (*n*=23) (%)	Gender (*n*)	ITP type	Outcome
No response	48, *n*=11	-	7 - Primary ITP 4 - Secondary ITP	2 discontinued because of serious adverse events 3 managed with IVIG 3 treated with rituximab 5 of 9 responded to TPO-RA and achieved CR
Partial response	22, *n*=5	Male - 2 Female - 3	-	3 developed thrombocytopenia 1 discontinued MMF and switched to TPO-RA 2 continued but received MMF with rituximab and intermittent DEXA
Complete response	30, *n*=7	Male - 5 Female - 2	-	6 maintained CR 1 lost CR and continued on MMF and TPO-RA (eltrombopag) as maintenance therapy

TPO-RA=Thrombopoietin receptor agonist, CR=Complete response, DEXA=Dexamethasone, MMF=Mycophenolate mofetil, ITP=Immune thrombocytopenia, IVIG=Intravenous immunoglobulin

Discussion

The treatment and management of severe ITP remains a clinical challenge as many of the available therapies are not supported by prospective randomized controlled trials. The use of acute therapies such as IVIG and/or steroids is acceptable. However, side effects associated with such therapies on long term use is a major concern and limitation. There is an extensive list of the second line of therapies for the treatment of severe ITP. However, there is a limited evidence to support.

To the best of our knowledge, this is the largest cohort of cases wherein patients were treated with a combination of MMF and DEXA, respectively. This study would play a key role in demonstrating the future treatment pathways in patients with severe ITP.

Second-line therapies for ITP include pulsed high-dose corticosteroids, danazol, azathioprine, cyclophosphamide, vincristine, dapsone, cyclosporin A, and MMF.[4,5] Many of these treatments were not been supported by randomized studies or any other supporting data. TPO mimetics are recently introduced and showing some promising results.[4] The ability of MMF to increase the platelet count in ITP patients has been previously reported.[4,14,15,17] In a study conducted by Ming *et al*. in 21 patients, who treated completely with daily dose of 1.5–2.0 g, MMF for a minimum of 12 weeks achieved an overall response of 62% (CR: 24%, PR: 29%, and minor response: 10%).[17] These results are comparable to our series of 23 patients, where 52% have responded to MMF and DEXA therapy, 30% achieved CR, and 21% have achieved PR. It was identified that the combination was more effective in patients with fewer prior treatments than the monotherapy.

We have also demonstrated that MMF and DEXA are more beneficial in patients with primary ITP, certainly in terms of complete remission. The role of MMF along with DEXA in inducing a partial remission in secondary ITP cases still remains important.

Depending on the disease complexity, multiple treatment options were considered in patients with ITP. By the end of the treatment period, depending upon the treatment opted and its clinical response – overall treatment cost, hospital stay (in days), and hospitalization charges will be varied largely [Table 3].

The limitations of this study are that the cohort represents a retrospective collection of all those selected to receive MMF and DEXA. A small number of patients in the study preclude its generalization to the whole population.

Conclusion

From our cohort of 23 patients, we have demonstrated a response to MMF and DEXA in more than 50% of cases, including patients refractory to multiple lines of therapy, and after many years from diagnosis. Emphasis should be given to the limited side effects and the relatively low therapeutic dose needed to achieve and maintain response in patients. There is a potential promise for those patients who have unfortunately failed to sustain remission with first-line agents. Even if MMF and DEXA do not induce complete remission, it may at least help to reduce steroid burden or indeed can be used in combination with other drugs (e.g., rituximab). As an easily available and economical choice, MMF and DEXA should be considered in the patient therapeutic pathway and formal trials documenting its response in a randomized prospective setting should be performed to confirm these findings.

This was a preliminary research, wherein the difference between those who responded and those who did not could not be made based on the type of previous therapies.

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Conflicts of interest
There are no conflicts of interest

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