10-22-2015

Effect of mycophenolate mofetil on the white blood cell count and the frequency of infection in systemic lupus erythematosus.

Ananta Subedi
Thomas Jefferson University

Laurence S. Magder
University of Maryland

Michelle Petri
Johns Hopkins University School of Medicine

HHS Public Access

Author manuscript

Rheumatol Int. Author manuscript; available in PMC 2017 July 10.

Published in final edited form as:

Rheumatol Int. 2015 October ; 35(10): 1687–1692. doi:10.1007/s00296-015-3265-6.

Effect of mycophenolate mofetil on the white blood cell count and the frequency of infection in systemic lupus erythematosus

Ananta Subedi[1], **Laurence S. Magder**[2], and **Michelle Petri**[3]

[1]Department of Medicine, Thomas Jefferson University Hospital, 833 Chestnut Street, Suite 701, Philadelphia, PA, 19107, USA

[2]Department of Epidemiology and Public Health, University of Maryland, 660 West Redwood Street, Baltimore, MD 21201, USA

[3]Division of Rheumatology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205, USA

Abstract

Leukopenia is a common manifestation of SLE. Addition of immunosuppressive therapy in a SLE patient who is already leukopenic is a clinical concern. It could worsen leukopenia, increase the risk of infection, or both. The aim of this study was to analyze the immediate effect of mycophenolate mofetil on the white blood cell count and the rate of infection in SLE patients. Two hundred and forty-four patients within the Hopkins Lupus Cohort who were newly started on mycophenolate mofetil were included in the study. The white blood cell count and interval infection history on the day mycophenolate mofetil was started were compared with the white blood cell count and interval infection history at the next visit. The study was based on 244 patients who began taking mycophenolate mofetil in the cohort. The study population included 47 % African Americans, 44 % Caucasians, and 9 % other ethnicities. There was a slight but not statistically significant increase in the white blood cell count (6.63 vs. 7.01), after starting mycophenolate mofetil. Patients with a baseline white blood cell count <3000/mm^3 did have a statistically significant increase in the white blood cell count after starting mycophenolate mofetil (2.57 vs. 5.13, $P = 0.0047$). We also found a statistically significant increase in the risk of bacterial infection (but not viral infection) after starting mycophenolate mofetil (4 vs. 9 %, $P = 0.0036$). Leukopenia does not worsen with mycophenolate mofetil. However, mycophenolate mofetil appears to slightly increase the rate of bacterial (but not viral) infection.

Keywords

Mycophenolate; Infection; Leukopenia

Correspondence to: Ananta Subedi.

Conflict of interest None.

Introduction

Leukopenia is a common manifestation of SLE, occurring in 18–36 % [1, 2]. Both the total white blood cell count and lymphocyte count are lower in SLE than in healthy controls [3]. Leukopenia is one of the hematological criteria in the 1982 Revised Criteria for Classification of Systemic Lupus Erythematosus [4] and in the 1997 update [5]. It is a "stand-alone" criterion in the Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) for systemic lupus erythematosus [6].

The SLE literature suggests a variable frequency of leukopenia with the use of mycophenolate mofetil. Dooley et al. [7] in the phase 3 trial of mycophenolate mofetil versus azathioprine for the maintenance therapy of lupus nephritis found no leukopenia with mycophenolate mofetil (0 with mycophenolate mofetil vs. 3.6 % with azathioprine, $P = 0.06$). Other studies, many of which were limited by small numbers of patients, reported a variable frequency of leukopenia due to mycophenolate mofetil, ranging from 3 to 37 % [8, 9].

Clinical trials and observational studies have demonstrated a higher frequency of infection in SLE patients on mycophenolate mofetil. Appel et al. [10] in an induction study of mycophenolate mofetil for lupus nephritis found infection as the most common adverse event in both study groups (68.5 % with mycophenolate mofetil; 61.7 % with intravenous cyclophosphamide; treatment difference 6.81%; 95 % CI −2.96 to 16.58 %; $P = 0.17$). Dooley et al. [7] also reported infection as the most common adverse event in the maintenance study of mycophenolate mofetil for lupus nephritis, with a rate of 79.1 % in the mycophenolate mofetil group and 78.4 % in the azathioprine group. In other smaller studies of mycophenolate mofetil for lupus nephritis, the reported frequency of infection varied from 11 to 50 % [11, 12].

Prospective data from the Hopkins Lupus Cohort provide an opportunity to assess the impact of starting mycophenolate mofetil on white blood cell counts and infection. This paper presents the results of an analysis comparing results from cohort visits before and after starting mycophenolate.

Methodology

Patients and methods

Since 1987, patients with SLE under the care of one rheumatologist at Johns Hopkins University School of Medicine were invited to participate in the Hopkins Lupus Cohort. Inclusion in the cohort was based on the clinical diagnosis of SLE by the principal investigator (MP). The Johns Hopkins University School of Medicine Institutional Review Board approved the study yearly. All participants gave written informed consent.

Since initiation of the cohort study in 1987, clinical and laboratory data were prospectively collected at each clinic visit in a systematic fashion, according to the Hopkins Lupus Cohort protocol. At cohort entry, basic demographic characteristics (date of birth, age at SLE onset, ethnicity, sex, years of education, combined annual household income) and presenting

clinical manifestations were recorded. Clinical manifestations were assessed through record review and patient interview and updated at each subsequent visit. Patients were seen at regular intervals of 3 months, or more frequently if medically indicated. At each patient visit, vital signs, a complete history, physical examination, and routine laboratory testing were performed. The complete white blood count was recorded at every visit, but not lymphocyte or neutrophil count. Mycophenolate mofetil doses ranged from 1000 to 3000 mg daily.

Definitions of infection—A detailed history of any infections since the last visit, including duration of symptoms and use of any antibiotic, was obtained. The start date of each infection was recorded. Medical records were reviewed to ascertain the type of interval infection. If the patient was symptomatic at a visit, a urine culture was ordered and a urinary tract infection was recorded only if positive. A chest X-ray was ordered, and only if abnormal was pneumonia diagnosed.

Statistical analysis

We compared the white blood cell count on the day of the visit when mycophenolate mofetil was started with the white blood cell count at the next visit, while the patient was continuing on mycophenolate mofetil. We also compared the frequency of interval and current infection at the visit before and after the start of use of mycophenolate mofetil. To assess the statistical significance of observed differences, adjusting for corticosteroid use (which is known to affect white blood cell count), we calculated *P* values based on generalized estimating equations.

All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

There were 244 patients who began taking mycophenolate mofetil while in the Hopkins Lupus Cohort. This included 114 (47 %) African American, 107 (44 %) Caucasian, and 23 (9 %) other ethnicities. Of these, 213 (87 %) were female and 31 (13 %) male (Table 1). The time between the two study visits ranged from 7 to 120 days, with a median of 47 days.

Table 2 shows the mean white blood cell count at the visit when mycophenolate mofetil was started and at the next visit. There was a slight increase in the white blood cell count on mycophenolate mofetil, which was not statistically significant. This was true in both Caucasians and African Americans. However, in those patients who started with a white blood cell count $<3000/mm^3$ before the start of mycophenolate mofetil, there was a statistically significant increase in the white blood cell count after starting mycophenolate mofetil. This significant association was seen in both Caucasians and African Americans when these groups were analyzed separately.

Table 3 demonstrates the change in the white blood cell count after adjustment for ethnicity and prednisone. African Americans were found to have a lower white blood cell count compared to Caucasians. Prednisone use was associated with a small but significant increase

in the white blood cell count. The effect of ethnicity was virtually eliminated in the analysis on mycophenolate mofetil.

Of the 19 patients who had a low white blood cell count (<3000/mm^3) prior to starting mycophenolate mofetil, 16 (84 %) had levels above 3000/mm^3 at the follow-up visit. Among the 225 who did not have low levels before starting mycophenolate mofetil, 11 (5 %) developed low white blood cell counts. Thus, there were fewer patients with low white cell counts at the follow-up visit [14] than before starting mycophenolate mofetil [19].

Table 4 shows the changes in white blood cell count by dose of mycophenolate mofetil. At every dose, there was a small, non-significant increase in the white blood cell counts.

We compared the visits before and after the start of mycophenolate mofetil with respect to the risk of interval and current infection (Table 5). There was a small, statistically significant risk of bacterial infection, but no increased risk of viral infection. The mean SLEDAI was lower at follow-up (mean = 4.7) than prior to starting MMF (5.9).

Discussion

We found, in SLE patients with baseline leukopenia (white blood cell count <3000/mm^3), there was a statistically significant increase in the white blood cell count. It is very unlikely that this improvement is due to regression to the mean. It is reassuring that on average, white blood cell counts increased after starting mycophenolate mofetil in this vulnerable set of patients. In previous studies, in SLE patients treated with mycophenolate mofetil, leukopenia was reported as a known side effect with variable frequency. Houssiau et al. [13] in the MAINTAIN Nephritis study, reported leukopenia in 4 % of the patients (n = 53) on mycophenolate mofetil. In another smaller study (n = 26) by Ong et al. [9], leukopenia was found in 37 % of the SLE patients on mycophenolate mofetil. The meta-analysis by Feng et al. [14] comparing mycophenolate mofetil with azathioprine for maintenance therapy of lupus nephritis showed less leukopenia with mycophenolate mofetil than azathioprine (RR 0.12; 95 % CI 0.04–0.39, P = 0.0004). Touma et al. [15] in their meta-analysis of patients with lupus nephritis found no statistical difference in the risk of leukopenia with mycophenolate mofetil compared to cyclophosphamide [RR 1.29 (0.35, 4.70)].

Our study was unique in that we compared the white blood cell count before and after the start of mycophenolate mofetil therapy. Our study design allowed the patients to be their own control. A limitation of our study was that we were not able to compare the effect of mycophenolate mofetil on the lymphocyte or neutrophil count, as differential counts were not part of the cohort protocol.

The major concern in SLE with mycophenolate mofetil, regardless of leukopenia or lymphopenia, is the impact of mycophenolate mofetil on infection risk. In our study, we found a statistically significant increase only in the frequency of bacterial infection in SLE patients on mycophenolate mofetil. Merrill et al. [16] in the phase III belimumab trial demonstrated that the rate of overall infection, including severe and serious infections, was higher in SLE patients on mycophenolate than on other immunosuppressives. The effect continued during the follow-up period of 4 years. The recent BELONG study, which

evaluated ocrelizumab in SLE patients with lupus nephritis, provided further insight into the infection risk of mycophenolate mofetil. Overall, the proportion of patients with infections was higher in those receiving background mycophenolate mofetil than in those receiving the background Euro-Lupus regimen (consisting of cyclophosphamide followed by azathioprine) [17]. Feng et al. [14] in their meta-analysis comparing mycophenolate mofetil with azathioprine for the maintenance therapy of lupus nephritis showed no significant difference in the risk of infection (RR 0.61, 95 % CI 0.14–2.68). Henderson et al. [18] found fewer major infection episodes among lupus nephritis patients on mycophenolate mofetil compared with oral cyclophosphamide (1 study, 62 patients; RR 0.21, 95 % CI 0.05–0.89), but not intravenous cyclophosphamide (6 studies, 683 patients; RR 1.11, 95 % CI 0.74–1.68). There was no difference in the risk of herpes zoster infection between the mycophenolate mofetil and the intravenous cyclophosphamide group (4 studies, 613 patients; RR 1.35, 95 % CI 0.71–2.58).

A limitation of our study is that the Hopkins Lupus Cohort visits were outpatient visits, but ascertainment of interval infection included any that occurred during an interval hospitalization, as well. We acknowledge the limitation that we do not have a ranking of the severity of infections reordered in the database. However, the bacterial infections were primarily urinary tract infection, bronchitis, sinusitis, and cellulitis. None of these infections required hospitalization or intravenous antibiotics. There was one case of progressive multifocal leukoencephalopathy (PML) in a patient taking mycophenolate mofetil, but after long use (not at first visit after starting), so it was not included in our analysis.

Based on the mechanism of action, mycophenolate mofetil preferentially inhibits the type II isoform of inosine-5′-monophosphate (IMPDH), which is expressed exclusively in activated T and B lymphocytes. We did not find any statistically significant difference in the frequency of viral infection. Our study demonstrates the increased risk of bacterial infection in SLE patients taking mycophenolate mofetil and emphasizes the importance of regular vaccination against the common infections including influenza and pneumococcus as recommended by the European League Against Rheumatism (EULAR) [19]. A careful screening for bacterial infections in febrile or symptomatic SLE patients at each visit on mycophenolate is warranted. In renal transplant patients on mycophenolate mofetil, viral infection is reported as more common, among which cytomegalovirus is a concern. The clinical trials of mycophenolate mofetil in SLE patients have not reported cytomegalovirus as a common infection nor did we have a single cytomegalovirus infection in our study. We cannot explain why we see more of a bacterial infection risk in our SLE population.

Conclusion

In conclusion, in a study design in which SLE patients served as their own control (before and during taking mycophenolate mofetil), mycophenolate mofetil did not result in a decrease in the white blood cell count. However, bacterial (but not viral) infections were significantly increased. The risk of infection from mycophenolate mofetil in SLE cannot be assessed by the white blood cell count alone and requires ongoing vigilance on the part of both the patient and clinician to ensure early detection and treatment of infection. However, our results suggest that mycophenolate mofetil can be started in SLE patients with baseline

leukopenia, with the expectation that the white blood cell count is likely to improve, not worsen.

Acknowledgments

The Hopkins Lupus Cohort is supported by a Grant from the National Institute of Health (NIH AR 43727). This publication was also made possible by Grant Number UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Road-map for Medical Research.

References

1. Rivero SJ, Diaz-Jouanen E, Alarcon-Segovia D. Lymphopenia in systemic lupus erythematosus. Clinical, diagnostic, and prognostic significance. Arthritis Rheum. 1978; 21(3):295–305. [PubMed: 646828]
2. Dias AM, do Couto MC, Duarte CC, Ines LP, Malcata AB. White blood cell count abnormalities and infections in one-year follow-up of 124 patients with SLE. Ann N Y Acad Sci. 2009; 1173:103–107. [PubMed: 19758138]
3. Erkeller-Yusel F, Hulstaart F, Hannet I, Isenberg D, Lydyard P. Lymphocyte subsets in a large cohort of patients with systemic lupus erythematosus. Lupus. 1993; 2(4):227–231. [PubMed: 8268970]
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982; 25(11):1271–1277. [PubMed: 7138600]
5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40(9):1725.
6. Petri M, Orbai A, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012; 64(8):2677–2686. [PubMed: 22553077]
7. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011; 365(20):1886–1895. [PubMed: 22087680]
8. Weng MY, Weng CT, Liu MF. The efficacy of low-dose mycophenolate mofetil for treatment of lupus nephritis in Taiwanese patients with systemic lupus erythematosus. Clin Rheumatol. 2010; 29(7):771–775. [PubMed: 20195879]
9. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology (Carlton). 2005; 10(5):504–510. [PubMed: 16221103]
10. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009; 20(5):1103–1112. [PubMed: 19369404]
11. Wang F, Wang N, Li J. Analysis on the infection among patients with nephrotic syndromes and systemic vasculitis treated with mycophenolate mofetil. Clin Rheumatol. 2010; 29(9):1073–1074. [PubMed: 20490590]
12. El-Shafey EM, Abdou SH, Shareef MM. Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? Clin Exp Nephrol. 2010; 14(3):214–221. [PubMed: 20169461]
13. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010; 69(12):2083–2089. [PubMed: 20833738]
14. Feng L, Deng J, Huo DM, Wu QY, Liao YH. Mycophenolate mofetil versus azathioprine as maintenance therapy for lupus nephritis: a meta-analysis. Nephrology (Carlton). 2013; 18(2):104–110. [PubMed: 23113811]

15. Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. J Rheumatol. 2011; 38(1):69–78. [PubMed: 20952473]

16. Merrill JT, Ginzler EM, Wallace DJ, McKay JD, Lisse JR, Aranow C, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum. 2012; 64(10):3364–3373. [PubMed: 22674457]

17. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum. 2013; 65(9):2368–2379. [PubMed: 23740801]

18. Henderson LK, Masson P, Craig JC, Roberts MA, Flanc RS, Strippoli GF, et al. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. Am J Kidney Dis. 2013; 61(1):74–87. [PubMed: 23182601]

19. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010; 69(7):1269–1274. [PubMed: 19892750]

Table 1

Characteristics of the study sample

Variable	Number (%)
Sex	
Female	213 (87)
Male	31 (13)
Race	
African American	114 (47)
Caucasian	107 (44)
Other	23 (9)
Age	
<30	74 (30)
30–44	107 (44)
45–59	52 (21)
60+	11 (5)
Days between visits	
<30	51 (21)
30–59	92 (38)
60–89	36 (15)
90–120	65 (27)
Prednisone dose at the time of the first visit	
0	53 (22)
1–9	53 (22)
10–19	59 (24)
20+	77 (32)
Using Prednisone at the time of the second visit	
0	32 (13)
1–9	48 (20)
10–19	65 (27)
20+	99 (41)

Table 2

Mean ± SD white blood cell count before and after start of mycophenolate mofetil

Patient group	Before mycophenolate mofetil (×1000 cells/mm^3)	After start of mycophenolate mofetil (×1000 cells/mm^3)	*P* value[a]
All patients (*n* = 244)	6.64 (3.45)	7.01 (3.40)	0.28
African American (*n* = 114)	6.22 (3.10)	6.57 (3.36)	0.67
Caucasian (*n* = 107)	7.25 (3.93)	7.35 (3.19)	0.77
Patients with white blood cell <3000/mm^3 at baseline (*n* = 19)	2.55 (0.37)	4.38 (1.42)	<0.0001

[a]Based on a model, which adjusted for corticosteroid use

Table 3

Mean WBC by prednisone dose and race, before and after starting of mycophenolate mofetil

Subgroup	Before starting MMF		After starting MMF	
	Mean (SD) WBC	*P* value	Mean (SD) WBC	*P* value
Prednisone dose				
None	5.02 (3.26)	<0.0001[a]	5.27 (2.21)	<0.0001[a]
1–9	5.97 (2.21)		5.46 (2.20)	
10–19	6.40 (3.29)		7.14 (3.80)	
20+	8.40 (3.72)		8.25 (3.41)	
Race/ethnicity				
Caucasian	7.25 (3.93)	0.0099[b]	7.35 (3.19)	0.049[b]
African American	6.22 (3.10)		6.57 (3.36)	
Other	5.92 (2.13)		7.64 (4.31)	

[a]Based on a model that assumes a linear relationship between prednisone dose and mean WBC adjusting for race/ethnicity

[b]Based on a model adjusting for prednisone dose

Table 4

Mean ± SD white blood cell count before and after start of mycophenolate mofetil, by dose

Dose[a]	Before mycophenolate mofetil (×1000 cells/mm^3)	After start of mycophenolate mofetil (×1000 cells/mm^3)	*P* value[b]
<1000 (*n* = 11)	5.68 (2.18)	6.64 (2.36)	0.14
1000–1500 (*n* = 69)	6.52 (3.65)	6.63 (3.14)	0.81
2000–2500 (*n* = 132)	6.85 (3.55)	7.24 (3.65)	0.30
3000 (*n* = 21)	6.97 (3.35)	7.32 (3.28)	0.76

[a] Dose information missing for 11 patients

[b] Based on a model, which adjusted for corticosteroid use

Table 5

Number (%) with infection[a] at the clinic visits immediately before and after start of mycophenolate mofetil

Variable	Before mycophenolate mofetil *n* (%)	After mycophenolate mofetil *n* (%)	Adjusted *P* value[b]
Infection (viral or bacterial)	33 (14 %)	46 (19 %)	0.0019
Viral infection	27 (11 %)	27 (11 %)	0.51
Bacterial infection	9 (4 %)	23 (9 %)	0.0036

[a] Most common infections: urinary tract infection, bronchitis, sinusitis, and cellulitis

[b] *P* value adjusted for prednisone dose