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# Toxicity and Efficacy of Daily Dapsone as *Pneumocystis jiroveci* Prophylaxis after Hematopoietic Stem Cell Transplantation: A Case-Control Study

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## ABSTRACT

**The toxicity and efficacy of dapsone given daily as *Pneumocystis jiroveci* (PCP) prophylaxis in hematopoietic stem cell transplant (HSCT) recipients who cannot take trimethoprim-sulfamethoxazole (TMP-SMX) have not been fully evaluated. We compared 155 HSCT recipients who received daily dapsone as second-line PCP prophylaxis with 310 matched control patients who received TMP-SMX throughout the posttransplantation course. Among patients who started dapsone before transplantation because of TMP-SMX allergy, there was no difference in the transfusion requirement after HSCT when compared with controls. Among patients who started dapsone after transplantation, increased red blood cell ($P < .0001$) and platelet transfusion ($P = .003$) requirements were noted compared with controls. This effect was, however, limited to patients who were receiving dapsone for reasons (mostly neutropenia) other than TMP-SMX allergy. Two of 155 patients developed PCP, compared with 0 of 310 controls ($P = .11$); both patients survived. In conclusion, the efficacy of daily dapsone in preventing PCP was similar to that observed in patients able to remain on TMP-SMX prophylaxis. Dapsone did not seem to cause hematologic toxicity among TMP-SMX–allergic patients. The observed higher transfusion need in patients who received dapsone for reasons other than TMP-SMX allergy seems mostly due to an underlying condition of poor marrow reserve. Further studies are required to establish whether the drug has an etiologic role in these situations.**


## KEY WORDS

*Pneumocystis jiroveci* • Dapsone • Hematopoietic stem cell transplantation

## INTRODUCTION

*Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP) is a serious and potentially life-threatening infection that can occur in an immunocompromised host and is one of the major concerns in patients who undergo hematopoietic stem cell transplantation (HSCT) [1-4]. However, prevention of PCP is also one of the greatest successes in the field of infection prophylaxis after HSCT. Indeed, its incidence was reduced from 8%-15% to 0.2% after the introduction of trimethoprim-sulfamethoxazole (TMP-SMX) as a prophylactic agent [5,6]. In addition, whereas in past decades this infection occurred mostly 40 to 80 days after transplantation, it is now rare and principally occurs after 6 months after transplantation [7]. Main risk factors are extensive chronic graft-versus-host disease (GVHD), ongoing corticosteroid use, and relapse of malignant disease [8].

The need for an alternative prophylactic agent ranges from 17% to 38%. The main reasons are intolerance/allergy and neutropenia [9,10]. There seems to be an increased need for alternative agents because of the increased use of drugs that may cause cumulative toxicities with TMP-SMX, such as ganciclovir or valganciclovir, mycophenolate mofetil, and imatinib.

Aerosolized pentamidine, dapsone, and, recently,

atovaquone [11] are the possible candidates for second-line therapy. In both human immunodeficiency virus (HIV)–infected individuals and HSCT recipients, aerosolized pentamidine has been associated with less protection than TMP-SMX [12-14]. Some studies, however, still suggest aerosolized pentamidine as a valid prophylactic agent in immunodeficiency [15-17] and post-HSCT settings [18-20]. A small study in pediatric marrow transplant recipients reported dapsone (50 mg/m$^2$ once a week) as a valid and well-tolerated agent for pediatric patients intolerant of TMP-SMX [21]. In a retrospective study conducted at our center, intermittent administration of dapsone (50 mg orally twice daily 3 times per week) as second-line prophylaxis was associated with high rates of breakthrough PCP after HSCT. The failure rate was 7.2%, with an associated relative risk for PCP of 18.8 ($P <$ .01) [10]. On the basis of this result, daily dosing was advocated [10]. The recommendation was supported by a randomized study conducted in HIV-infected subjects [22]. However, few data exist on the toxicity of daily dapsone used as second-line prophylaxis after HSCT. Vasconcelles et al. [13], in a retrospective cohort study, confirmed that TMP-SMX is superior to aerosolized pentamidine as primary prophylaxis after HSCT and also showed that a limited group of 31 patients treated with daily dapsone (100 mg/d) did not have a significantly increased probability of PCP or death compared with those treated with TMP-SMX. The toxicity rate was higher than that with standard treatment, and hemolytic reactions were the greatest concern. Additional dapsone side effects include intolerance/allergy, methemoglobinemia, gastrointestinal adverse events, and myelosuppression [13]. The dapsone hydroxylamine metabolite is considered to be responsible for the hemolytic effects; it leads to a loss of erythrocytic glutathione content [23,24]. Screening patients for glucose-6-phosphate dehydrogenase (G6PD) deficiency is advised before the drug is started [25] and could help prevent hemolytic reactions. The clinical relevance of hemolytic anemia has been poorly evaluated. Indeed, no data are available on the transfusion requirements after dapsone administration.

We conducted a retrospective case-control study to evaluate the toxicity and efficacy of daily dapsone (50 mg twice daily) as second-line PCP prophylaxis in patients undergoing HSCT. We investigated the clinical relevance of hematologic toxicity, especially in terms of transfusion requirements, and the incidence of PCP and other relevant infections.

## METHODS

### Patients

We conducted a retrospective matched control study on 155 patients who underwent HSCT at the Fred Hutchinson Cancer Research Center (FHCRC; Seattle, WA) between 1998 and 2001 and who received daily dapsone as PCP prophylaxis for more than 1 week by day +100 after transplantation. Patients who were already discharged from the FHCRC or those who had experienced leukemic relapse before starting their prophylaxis were excluded. Dapsone recipients (cases) were divided into 2 groups according to whether prophylaxis with dapsone was given for the first time before or after HSCT.

Each case was matched with 2 control patients who received standard TMP-SMX prophylaxis. Matching criteria were the type of HSCT (autologous or syngeneic; allogeneic/myeloablative versus allogeneic/nonmyeloablative) and donor type (related versus unrelated). The transplantation date in control patients was as close as possible to that of their corresponding cases.

Control patients also had to be alive and free from leukemic relapse at least as long as the start date of dapsone in their corresponding cases. The study was approved by the FHCRC Institutional Review Board.

### Prophylaxis Regimen

PCP prophylaxis was given according to FHCRC internal clinical practice guidelines. The recommended standard treatment with TMP-SMX started in the pretransplantation period, upon admission for HSCT, with 1 double-strength tablet (800 mg of sulfamethoxazole and 160 mg of trimethoprim) twice daily orally, was discontinued 48 hours before transplantation, and was generally reintroduced in the posttransplantation period when the absolute neutrophil count (ANC) is >500/mm$^3$ for 3 days. Patients who were allergic to TMP-SMX were generally referred to desensitization [10].

If TMP-SMX could not be administered by day +30 or if desensitization failed, the use of alternative prophylaxis was recommended, and dapsone (50 mg orally twice daily) was considered the second-line treatment. The dose was divided into 2 daily administrations to avoid a high peak serum level that may correlate with hematologic toxicities (median day −17). For pediatric patients, the dose was adjusted to 1 mg/kg/d in 2 divided doses (up to 100 mg/d). When started before HSCT, upon admission for HSCT (based on unpublished results by the manufacturer), dapsone was recommended to be discontinued 2 days before stem cell infusion and during the initial transplantation period, as was done for TMP-SMX. Prophylaxis with dapsone was not given if G6PD deficiency was found in the recipient [25].

Both standard and second-line prophylaxis were continued for at least 6 months after transplantation or for as long as patients had evidence of clinical extensive chronic GVHD or continued to receive sys-

temic immunosuppressive therapy. Patients receiving dapsone were also prescribed penicillin VK (750 mg twice daily).

### Toxicity

Red blood cell (RBC) and platelet transfusion requirements were evaluated after medication for patients who had dapsone only in the posttransplantation period and after HSCT for patients who started their dapsone prophylaxis before HSCT. Patient clinical and laboratory data were collected until discharge date, death, relapse, or subsequent transplantation. Transfusion requirements were expressed as units required per 100 days of follow-up (time from HSCT or dapsone start to the earliest of the above-mentioned end points). The results were stratified into 2 groups according to the reason for starting dapsone (allergy/intolerance to TMP-SMX versus other reasons). Results were adjusted for other factors potentially associated with transfusion requirements, such as major ABO mismatch and severe GVHD (grade III or IV). All cases and controls were well balanced with respect to stem cell source (bone marrow versus peripheral blood stem cells). The cumulative incidence for liver (aspartate aminotransferase and alanine aminotransferase >200 IU/L and bilirubin >2 mg/dL), renal (creatinine >1.5 mg/dL), or hematologic (haptoglobin <100 mg/dL, hemoglobin <8 g/dL, hematocrit <24%, and lactate dehydrogenase >400 IU/L) toxicity after medication was evaluated only in patients who received dapsone for the first time in the post-HSCT setting . Toxicity data were analyzed until death, discharge, relapse, subsequent transplantation, or day +100 after HSCT, whichever came earlier, and were adjusted for age, severe GVHD, major ABO mismatch, and stem cell source. Summaries from clinical records were reviewed to identify episodes of intolerance or toxicity leading to the drug suspension.

### Efficacy

Efficacy was evaluated by the incidence of PCP in the 2 groups at any time after HSCT. The incidence of PCP was also evaluated in the entire transplant population during the study period. Infection data after discharge from Seattle were obtained by using the long-term follow-up database. This database includes results from annual surveys on symptoms and complications, transcripts of telephone consultations, copies of clinic notes, hospital admission and discharge reports, and death reports. Diagnoses of PCP were accepted only if clinical records documented PCP in clinical specimens. Incidence figures for invasive pneumococcal pneumonia infection, nocardiosis, toxoplasmosis, and *Haemophilus influenzae* and *parainfluenzae* infections at any time after HSCT were also collected.

### Statistical Analysis

Descriptive statistics such as median, 25th and 75th percentiles, and range were calculated as appropriate. Transfusion requirements were adjusted for days of follow-up. Adjusted transfusion requirements were compared between groups by the Wilcoxon 2-sample test. The analysis was stratified according to the reason for starting dapsone (TMP-SMX allergy versus other reasons). Analysis of variance on ranked adjusted transfusion values was used to adjust for major ABO mismatch, GVHD, and other possible confounders. Cumulative incidence curves for toxicity measures were plotted by using methods previously described [26]. Statistical comparisons of the toxicity measures between groups were based on likelihood ratio statistics from Cox proportional hazard models, which included adjustment for possible confounding factors. The rates of PCP and other infections were compared between groups by Fisher exact test. All *P* values are 2 sided.

## RESULTS

One hundred seventy-three patients were identified who received daily dapsone before day +100 after transplantation (Table 1). Thirteen patients who received dapsone after HSCT for less than 1 week were excluded. These patients were switched back to standard therapy after transient neutropenia, toxicity, or TMP-SMX desensitization (n = 7), if they experienced intolerance or toxicity associated with dapsone (n = 3), or without a clear reason noted in the chart (n = 3). Three patients who were discharged from the FHCRC, and 2 who experienced leukemic relapse before prophylaxis started were excluded. A final number of 155 cases were evaluated for the study and compared with a group of 310 controls. Baseline characteristics are shown in Table 1. Overall, approximately 10% (155 of 1512 patients who underwent transplantation) of patients received dapsone during the first 3 months after transplantation.

Cases and controls were well matched (Table 1). However, patients who started dapsone after transplantation had a lower ANC and platelet count than controls receiving TMP-SMX. When stratified by the reason for dapsone administration, no difference was apparent in those in whom dapsone was given for TMP-SMX allergy (Table 1), thus suggesting that the difference was driven by those in whom dapsone was given for an underlying poor marrow reserve.

The median overall follow-up (time from prophylaxis start to date of last contact) was 29 months for cases (range, 0.3-72.6 months) and 28.9 for controls (range, 0.1-65.5 months). Allergy to TMP-SMX and situations of depressed marrow function were the

**Table 1.** *Baseline Characteristics of All Patients, Acute GVHD Incidence, and Engraftment Data*

| Variable | Dapsone (n = 155) | Controls (n = 310) |
|---|---|---|
| **Age at transplantation, y, median (range)** | **44 (1–70)** | **44 (1–68)** |
| **Sex** | | |
| **Male** | **62 (40%)** | **165 (53%)** |
| **Female** | **93 (60%)** | **145 (47%)** |
| **Race** | | |
| **Caucasian** | **133 (86%)** | **254 (82%)** |
| **Other** | **22 (14%)** | **56 (18%)** |
| **Main diagnosis** | | |
| **Hematologic malignancy** | **138 (89%)** | **270 (87%)** |
| **Other** | **17 (11%)** | **40 (13%)** |
| **Stem cell source** | | |
| **BM** | **63 (41%)** | **127 (41%)** |
| **PBSC** | **90 (58%)** | **175 (56%)** |
| **BM + PBSC** | **0 (0%)** | **3 (1%)** |
| **Cord blood** | **2 (1%)** | **5 (2%)** |
| **Donor type** | | |
| **Autologous/identical twin** | **31 (20%)** | **63 (20%)** |
| **Related** | **60 (39%)** | **117 (38%)** |
| **Unrelated** | **64 (41%)** | **130 (42%)** |
| **Conditioning regimen** | | |
| **Myeloablative** | **139 (90%)** | **279 (90%)** |
| **Nonmyeloablative** | **16 (10%)** | **31 (10%)** |
| **ABO mismatch (6 unknown)** | | |
| **Matched** | **120 (80%)** | **251 (81%)** |
| **Mismatched** | **30 (20%)** | **58 (19%)** |
| **Acute GVHD*** | | |
| **Grade 0–II** | **92 (74%)** | **187 (77%)** |
| **Grade III/IV** | **32 (26%)** | **57 (23%)** |
| **Gut GVHD[1]** | | |
| **Grade III** | **3 (2%)** | **11 (5%)** |
| **Grade IV** | **3 (2%)** | **11 (5%)** |
| **ANC ($\times 10^9$/L) at dapsone start, median (range)†** | | |
| **No TMP-SMX allergy** | **1.9 (0–16.5)‡** | **3.6 (0–20.9)‡** |
| **TMP-SMX allergy** | **3.4 (0.3–11.2)** | **3.8 (0–18.7)** |
| **PLT ($\times 10^9$/L) at dapsone start, median (range)†** | | |
| **No allergy** | **49 (4–232)‡** | **104 (16–366)‡** |
| **Allergy** | **80 (14–275)** | **87 (7–383)** |

BM indicates bone marrow; PBSC, peripheral blood stem cells; PLT, platelets.

*Excluding autologous and syngeneic donor (and ungraded).

†Among those starting dapsone after transplantation.

‡$P < .0001$.

most frequently reported reasons for alternative PCP prophylaxis (Table 2).

## Toxicity

A higher probability of a decrease in hemoglobin level (≤8 g/dL) after medication was observed for patients who received dapsone for the first time in the posttransplantation setting compared with controls (adjusted $P = .02$). After a stratified analysis, the result was no longer significant for patients allergic to TMP-SMX ($P = .54$; Figure 1). No significant differences were observed for liver enzymes (aspartate aminotransferase or alanine aminotransferase), serum creatinine, lactate dehydrogenase, haptoglobin, or hematocrit abnormalities (data not shown).

Clinical adverse effects with dapsone use were reported in 19 (12%) of 155 cases and included intolerance or allergy (n = 5), hemolysis (n = 9), and hemolysis with methemoglobinemia (n = 5). This led to discontinuation or temporary suspension of dapsone in 16 cases (10%). None of these episodes was described as life threatening. Eleven of the hemolytic events induced the clinician to suspend dapsone, resulting in a resolution or improvement in 8 cases; 3 patients did not have a clear beneficial effect after drug removal. Hemolysis did not require dapsone suspension in 3 episodes, either because they were thought to be mostly due to ABO mismatch (n = 2) or because they were defined as mild and resolved when TMP-SMX was reintroduced after a temporary condition of depressed marrow function. A G6PD deficiency is unlikely to be the reason for the reported hemolytic episodes because, according to our guidelines, all patients had a normal G6PD value before they started dapsone.

## Transfusion Requirement

Among the 116 patients who started dapsone after HSCT (median, day +51; range, 16-91 days), there was a higher RBC and platelet transfusion requirement compared with controls. Results were adjusted for major ABO mismatch and severe GVHD (Table 3). After stratifying the analysis according to the reason why second-line PCP prophylaxis was required (TMP-SMX allergy versus no allergy), we observed

**Table 2.** *Reasons for Use of Dapsone as Secondary PCP Prophylaxis*

| Reason for Dapsone | Dapsone Start before HSCT (n = 39) | Dapsone Start after HSCT (n = 116) | Total Cases (n = 155) |
|---|---|---|---|
| **TMP-SMX allergy** | **35 (90%)** | **48 (41%)** | **83 (54%)** |
| **Poor marrow function** | **0** | **47 (41%)** | **47 (30%)** |
| **Liver toxicity** | **0** | **6 (5%)** | **6 (4%)** |
| **Renal toxicity** | **0** | **5 (4%)** | **5 (3%)** |
| **Not reported** | **4 (10%)** | **10 (9%)** | **14 (9%)** |

Results are divided into 2 groups according to whether dapsone was started for the first time before transplantation (after admission) or in the posttransplantation period. Among patients who were not allergic to TMP-SMX poor marrow function was the main reason for secondary PCP prophylaxis with dapsone.

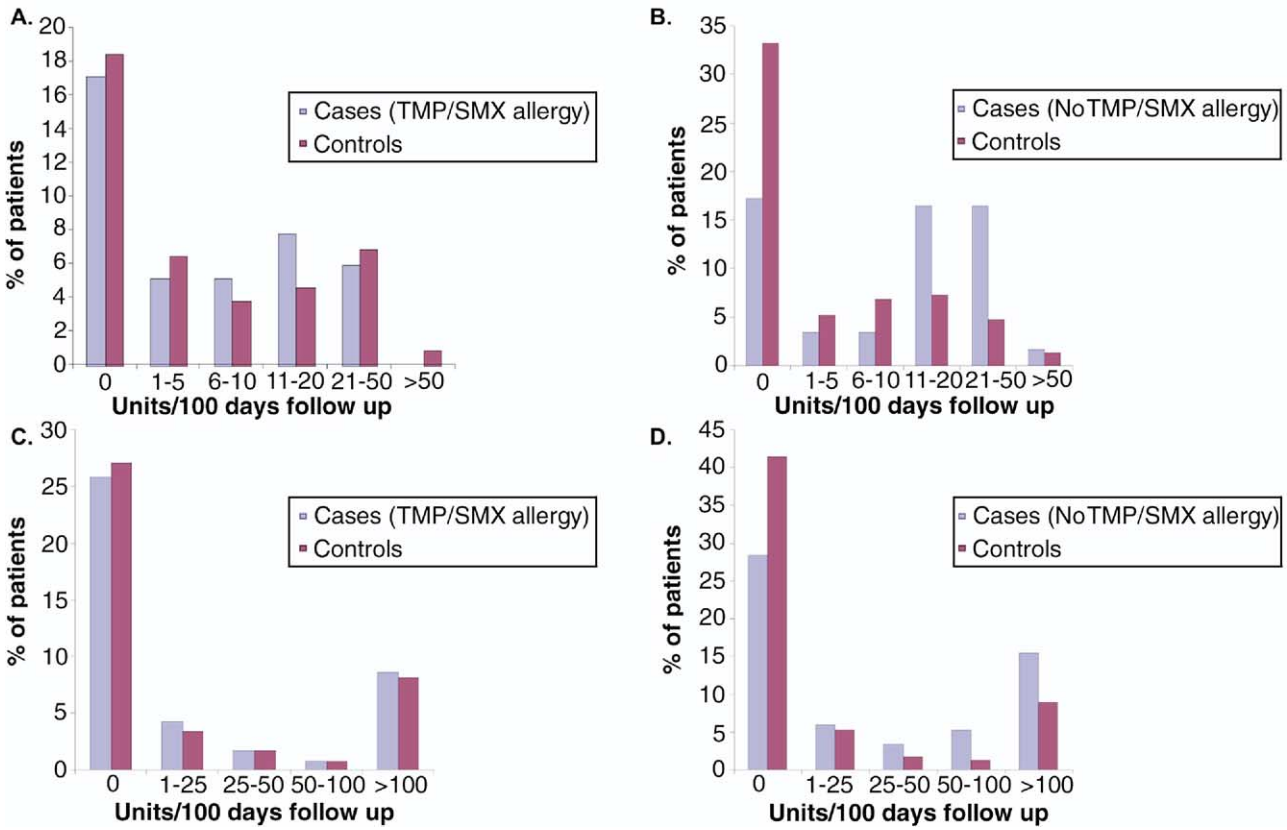


**Figure 1.** Distribution of red blood cell (A and B) and platelet (panels C and D) transfusions for patients who started dapsone for the first time after HSCT (n = 116) and their corresponding controls (n = 232) . Results are expressed as number of units/100 days of follow-up and are grouped according to the reason for dapsone secondary prophylaxis (TMP-SMX allergy versus no allergy).

that a higher need for RBC and platelet transfusions was limited to patients who received dapsone for reasons other than TMP-SMX allergy, mostly poor graft function or hematologic toxicity associated with TMP-SMX (Table 3). This group of patients had a higher need for transfusion support than controls, even before the prophylaxis started, and this suggests a poor graft function at the start of drug. The medians for 100 days of RBC and platelet transfusion units were in fact 10.5 and 11.5 versus 0 in the control group ($P = .003$ and $P = .005$, respectively). ANC and platelet counts at the time of prophylaxis start were also significantly lower ($P < .0001$) compared with controls (Table 1). Patients whose reason for dapsone was an allergy or intolerance to TMP-SMX had a transfusion requirement similar to that of controls (Table 3). The distribution of RBC and platelet transfusions among patients who started their second-line prophylaxis after HSCT is shown in Figure 2. The group of 39 patients who started their dapsone before HSCT did not have a significant difference in RBC or platelet requirements after transplantation compared with controls. Their medians for RBC and platelet transfusion units per 100 days of follow-up were 12 and 41, versus 12.5 and 65.5 among controls ($P = .67$ and $P = .26$, respectively). Thirty-five of these patients were found to be allergic to TMP-SMX, and in 4 cases the reason for dapsone was not clearly reported (Table 2).

### Efficacy

Two of 155 cases (1.3%; 95% confidence interval, 0.35%-4.6%) were diagnosed with PCP, whereas none of the 310 controls (0%; 95% confidence interval, 0%-1.2%) developed the infection. The difference was not statistically significant ($P = .11$; Table 4). When all patients who received TMP-SMX during the study period were analyzed, the incidence was 5 (0.37%; 95% confidence interval 0.16% to 0.86%) of 1357. When compared with the dapsone group, this also did not reach statistical significance ($P = .16$). Both patients who developed PCP after dapsone received a nonmyeloablative conditioning regimen; the first was from a related donor after an autologous graft (2 months earlier) as treatment for a multiple myeloma, and the second was from an unrelated donor for non-Hodgkin lymphoma that relapsed 3 years after a previous autologous transplantation. The PCP diagnoses were made at 7.5 and 11 months after HSCT. At that time, both patients were taking dapsone as prescribed. Immunosuppressive therapy included corticosteroids

and cyclosporin A in both patients. The first had a diagnosis of stable chronic GVHD and a partial graft failure with persistent partial (50%) donor T-cell engraftment; the second had a recent increase of the cyclosporin A dose after initial tapering because of GVHD development. Both patients responded to treatment with intravenous pentamidine.

Among the cases receiving dapsone that were reviewed for this study, we found 1 patient with a pneumocystis lung granuloma during the pretransplantation evaluation while not receiving any specific prophylaxis. Among controls, there was also 1 patient with PCP approximately 2 months before transplantation, before the prophylactic regimen with TMP-SMX started. Neither patient had any recurrence of PCP after transplantation.

The incidence of infections with encapsulated microorganisms or nocardia species seemed higher among patients who required dapsone (n = 12) prophylaxis when compared with controls (n = 9; $P$ = .03; Table 4). However, by the time that the infectious event occurred (cases: median, 8.5 months; range, 2-55 months after HSCT; controls: median, 6 months; range, 2-31 months after HSCT), only 6 of these 12 cases were still taking an alternative PCP prophylaxis that did not consist of TMP-SMX (2 dapsone and 4 pentamidine). Five of the remaining patients were switched back to TMP-SMX, whereas 1 had the infection before the second-line prophylaxis started.

No information was available regarding whether penicillin or other drugs for encapsulated bacteria were administered. Among those who restarted TMP-SMX, it is not known whether they received daily or intermittent doses.

## DISCUSSION

We conducted a retrospective matched case-control study of 155 patients who underwent HSCT at the FHCRC in Seattle over 4 years to investigate hematologic toxicity and the efficacy of daily dapsone as second-line PCP prophylaxis . A higher RBC and platelet transfusion requirement was observed only in patients who were switched from TMP-SMX to dapsone after transplantation for reasons other than TMP-SMX allergy (mainly for poor marrow function). No differences in toxicity were observed among patients who started their second-line PCP prophylaxis before HSCT or after HSCT because of allergy or intolerance to TMP-SMX. We found that daily dapsone had efficacy similar to that of the standard regimen with TMP-SMX in preventing PCP infections, although the sample size was too small to detect small differences. Patients who required alternative prophylaxis seemed to have a trend toward a higher incidence of other infections typically prevented by TMP-SMX. The major concern about dapsone administration is the possible development of hemolytic reactions [13]. We decided to focus on the clinical relevance of possible hemolytic events, which are ultimately the need for transfusions. A common reason for using alternatives to TMP-SMX is neutropenia, which indicates poor marrow function of the host rather than a drug effect. This could select a popula-

**Table 3.** *Transfusion Requirement Expressed in Number of Units per 100 Days of Follow-Up among Patients Who Started Dapsone after Transplantation*

| | Red Blood Cells | | | Platelets | | |
|---|---|---|---|---|---|---|
| **Variable** | **Dapsone** | **Controls** | ***P* Value** | **Dapsone** | **Controls** | ***P* Value** |
| **All patients** | | | | | | |
| **n** | 116 | 232 | | 116 | 232 | |
| **Median units/100 d** | 10.0 | 0.0 | .0003* | 0.0 | 0.0 | .02* |
| **Q1-Q3‡** | 0-20 | 0-11 | .0002† | 0-79 | 0-19 | .01† |
| **Range** | 0-190 | 0-121 | | 0-1210 | 0-1231 | |
| **Dapsone for TMP-SMX allergy** | | | | | | |
| **n** | 48 | 96 | 48 | 96 | | |
| **Median units/100 d** | 4.0 | 3.5 | .65* | 0.0 | 0.0 | .77* |
| **Q1-Q3‡** | 0-15 | 0-13 | .82† | 0-49 | 0-34 | .94† |
| **Range** | 0-43 | 0-100 | | 0-326 | 0-1231 | |
| **Dapsone for reasons other than TMP-SMX allergy** | | | | | | |
| **n** | 68 | 136 | 68 | 136 | | |
| **Median units/100 d** | 12.0 | 0.0 | <.0001* | 11.0 | 0.0 | .003* |
| **Q1-Q3‡** | 0-23 | 0-10 | <.0001† | 0-129 | 0-13 | .002† |
| **Range** | 0-190 | 0-121 | | 0-1210 | 0-886 | |

Results are shown for all cases and controls and are stratified according to the reason for dapsone second-line prophylaxis (TMP-SMX allergy versus no allergy).

*Adjusted for severe (grade III–IV) acute GVHD and major ABO mismatch.

†Unadjusted *P* value.

‡Q indicates interquartile range.

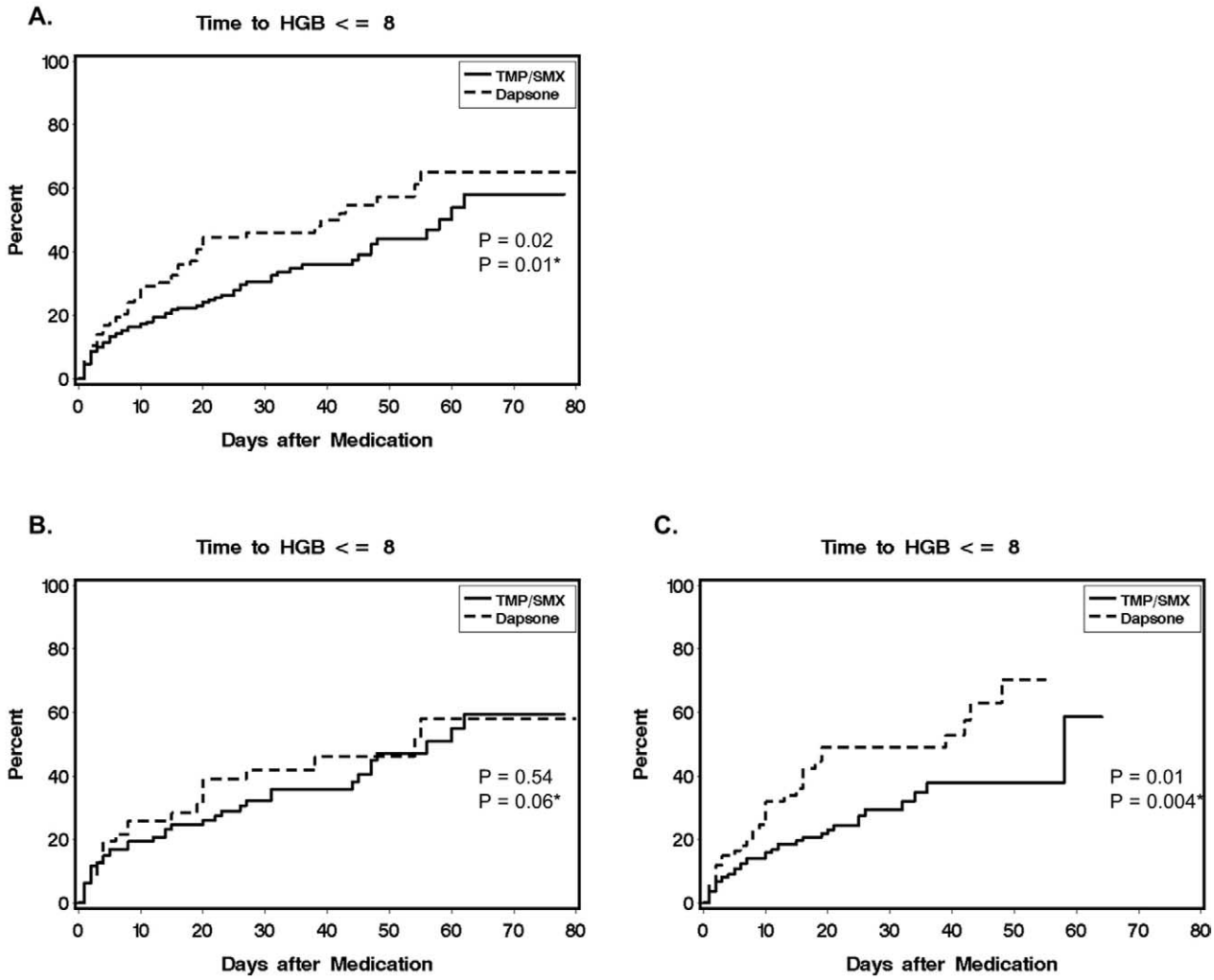


**Figure 2.** Cumulative incidence curves of hemoglobin (HGB) decrement (≤8 g/dL) for patients who started dapsone for the first time after transplantation (n = 116) and their corresponding controls (n = 232). Results are shown for all cases and controls (A) and stratified according to the reason for dapsone secondary prophylaxis: TMP-SMX allergy (B) versus no allergy (C). *P* values are adjusted for severe acute GVHD, major ABO mismatch, stem cell source, and age. *Unadjusted *P* values.

tion of patients with an independent higher transfusion need. We therefore stratified our analysis according to the reason why a second-line PCP prophylaxis was started. We found that 83 patients were treated with dapsone because of allergy to TMP-SMX; 35 started before HSCT, and 48 received the drug only after HSCT. The number of transfusions in these 2 groups was similar to that observed in their corresponding controls. However, patients who required PCP prophylaxis with daily dapsone for reasons other than TMP-SMX allergy after HSCT had a significantly higher need for transfusion compared with controls. This suggests that there was preexisting poor marrow function in these patients. Indeed, their transfusion need was higher than that of controls even in the period between HSCT and the start of dapsone. In addition, the ANC and platelet count at the time prophylaxis started also suggested poor graft function.

**Table 4.** *Infection Incidence at Any Time after HSCT for All Cases and Controls*

| Variable | Dapsone (n = 155) | Controls (n = 310) |
|---|---|---|
| ***Haemophilus* species** | 3 (2%)* | 2 (1%) |
| **Toxoplasmosis** | 1 (1%) | 0 (0%) |
| ***Streptococcus pneumoniae*** | 7 (5%)* | 5 (2%) |
| ***Nocardia* species** | 1 (1%) | 2 (1%) |
| **PCP** | 2 (1%) | 0 (0%) |
| **Any of the above (excluding PCP)** | 12 (8%) | 9 (3%)† |

The median time of infection (excluding PCP) incidence was 8.5 months after HSCT (range, 2-55 months) for cases and 6 months (range, 2-31 months) for controls.

*Two independent infectious episodes of *Haemophilus influenzae* and *Streptococcus pneumoniae* occurred in the same patient.

†*P* = .03.

Even if drug-associated toxicity had a probable role, this was certainly not the only cause. The fact that platelet requirements were also increased lends further support to this hypothesis, because dapsone is not believed to affect platelet number and function. Analysis of laboratory parameters indicative of possible hemolysis, including hematocrit, haptoglobin, and lactate dehydrogenase, did not show significant differences with the controls. The finding of a higher cumulative incidence of hemoglobin decrements only in patients who were not allergic to TMP-SMX also supports the hypothesis of the underlying poor marrow reserve as the main cause for the higher transfusion requirement. It should be mentioned, however, that 12% of the cases had a reported clinical adverse effect associated with dapsone, and this led to drug discontinuation or temporary suspension in 10%.

Our findings on efficacy are consistent with what has been observed in HIV patients, in whom only daily dapsone gave effective protection against pneumocystis. It also confirms the report by Vasconcelles et al [13]. The low incidence of PCP infections in the TMP-SMX group was consistent with what we have observed in previous studies, where it was 0.37% [10]. The incidence in the dapsone group (1.3%) seemed lower than that previously reported (7.2%) with intermittent administration [10], suggesting that the daily dose can make a difference. The development of PCP late after HSCT (7.5 and 11 months) in 2 patients treated with dapsone was consistent with the new trend observed with PCP infections after HSCT. However, the reasons for breakthrough are unknown. Poor adherence to the prophylactic regimen does not seem to be a factor. Another hypothesis could be a strain of pneumocystis that is resistant to dapsone, a defect in the intestinal absorption of the drug, or some unknown pharmacologic interaction. A trend toward a higher incidence of other encapsulated organisms and nocardia was observed in patients who required second-line PCP prophylaxis with dapsone compared with controls. Because dapsone does not provide sufficient coverage against encapsulated infections, additional antibacterial prophylaxis (eg, penicillin VK) is recommended according to Centers for Disease Control guidelines [25]. However, we could not obtain sufficient information about the adherence to penicillin-based antimicrobial prophylaxis. Of the 12 patients who developed such infections after HSCT, only 6 were actually receiving second-line PCP prophylaxis at the time the infectious event occurred, 2 still with dapsone, and 4 were switched to pentamidine because of dapsone toxicity. Of the remaining patients, 5 had been switched back to TMP-SMX, and 1 developed the infection before he started the second-line prophylaxis. Nevertheless, the trend toward a higher incidence of other infections emphasizes the need for additional prophylaxis aimed at these organisms [25].

We conclude that a prophylactic regimen of daily dapsone (50 mg twice daily) among patients who used it because of TMP-SMX allergy is not associated with a higher toxicity or transfusion requirement compared with matched controls. Thus, it may be considered a valid second-line agent. Significantly increased hematologic toxicity and need for transfusion support were observed in the group of patients who were switched from TMP-SMX to dapsone for reasons other than allergy, mainly for poor marrow reserve. Our study cannot conclusively determine whether the increased toxicity is due to preexisting poor graft function. It is possible that dapsone is more toxic in this setting; however, a randomized trial is needed to determine whether the drug itself might have an etiologic role in these situations. Dapsone intolerance leading to drug discontinuation or temporary suspension occurred in 10% of patients. The efficacy of daily dapsone in preventing PCP infections after HSCT was confirmed to be similar to that observed in controls receiving TMP-SMX, but a trend toward more breakthrough infections of other microorganisms not covered by dapsone was observed. Overall, the daily regimen seemed to be superior to intermittent dapsone, which was shown to be ineffective in an earlier study [10].

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