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Dapsone safety in haematology patients: pathways to optimising *Pneumocystis jirovecii* pneumonia prophylaxis in haematology malignancy and transplant recipients.

Short running title: Dapsone safety in haematology patients

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Abstract:

Dapsone may be used for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in haematology patients receiving immunosuppressive therapy or after hematopoietic stem cell transplant (HSCT) in the setting of trimethoprim-sulfamethoxazole (TMP-SMX) adverse drug reaction (ADR) history. Dapsone-induced haematological toxicities such as oxidative haemolysis may limit use in these patients and modern assessments of dapsone allergy cross-reactivity in non-HIV patients with a sulphonamide allergy are largely absent. The aim of this single-centre, retrospective study was to describe dapsone usage in haematology patients requiring PJP prophylaxis, including HSCT recipients, over a 12-month period in terms of indications, incidence of dapsone-attributed oxidative haemolysis, and immune cross-reactivity in those previously labelled with a sulphonamide allergy, as well as describing potential opportunities for first-line TMP-SMX PJP prophylaxis reintroduction. Out of 24 patients meeting the study inclusion criteria, 12 (50%) were receiving dapsone PJP prophylaxis post-HSCT. No cases of breakthrough PJP infection were noted. Sixteen patients (67%) were initiated on dapsone to avoid the perceived risk of further myelosuppression with TMP-SMX and 5 patients (21%) due to prior delayed immune-mediated allergy to TMP-SMX. None experienced rash with dapsone therapy. Six patients (25%) were successfully rechallenged on TMP-SMX, including one patient with prior TMP-SMX-associated rash. Four (17%) patients had confirmed oxidative haemolysis, all resulting in dapsone cessation. Dapsone PJP prophylaxis in haematology patients was effective and safe, with non-life threatening dapsone-related haemolysis noted in a small number. An absence of sulphonamide allergy cross-reactivity was noted, suggesting greater TMP-SMX rechallenges or desensitisation could be considered in those receiving dapsone.

Keywords: dapsone, adverse drug reactions, *Pneumocystis jirovecii* pneumonia, haematopoietic stem cell transplantation**Introduction:**

Dapsone is recommended as a second-line agent for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in the setting of a trimethoprim-sulfamethoxazole (TMP-SMX) adverse drug reactions (ADR) history[1, 2]. Whilst reports of dapsone cross-reactivity in TMP-SMX allergic patients is up to 20%[3-5], modern assessments of dapsone tolerability in non-HIV patients with an antibiotic sulphonamide allergy are largely absent. Dapsone is associated with haematological ADRs including oxidative haemolysis, particularly in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients and at higher doses[6, 7]. Incidence may be higher in haematology patients due to limited bone marrow reserve. Screening of patients for G6PD deficiency is recommended prior to

commencement[1, 2]. Here, we describe dapsone usage in our cohort of patients with haematological conditions requiring PJP prophylaxis, including haematopoietic stem cell transplant (HSCT) recipients, to better understand its real-world safety profile and indications for use, immune cross-reactivity in those previously labelled as sulphonamide allergic, and subsequently potential opportunities for conversion to first-line PJP prophylaxis with TMP-SMX.

Patients and Methods:

This was a retrospective study of patients with haematological conditions, including HSCT recipients (autologous and allogeneic) at Austin Health (Melbourne, AUS), receiving dapsone PJP prophylaxis. Haematology patients were identified from dispensing records if they had received dapsone between 1 November 2016 and 31 October 2017 inclusive. Patients were excluded if they received less than 7 days of dapsone or were not followed up by the Austin Health Haematology unit. Data collected included: patient characteristics, allergy history, dapsone course details, haemoglobin pre- and during dapsone course, G6PD levels (if tested), presence of oxidative haemolysis as documented in patient notes and/or on blood film, and management of cases. Cases with documented oxidative haemolysis were independently reviewed by a haematopathologist not involved in the original diagnosis (JW). Haemolysis was deemed dapsone-related if it was temporally related, resolved with cessation, and there were no other obvious causes. Common TMP-SMX ADRs were categorized as either Type-A (non-immune-mediated) or Type-B (immune-mediated) according to standard definitions[8]. Following accurate TMP-SMX ADR phenotyping, patients could undergo either TMP-SMX rechallenge, desensitization or continued avoidance as per our previously published protocol, developed in consultation with an external expert who leads an international antibiotic allergy service[9]. Patients with a history of mild delayed TMP-SMX hypersensitivity (Type-B), real/perceived myelosuppression risk, or other Type-A TMP-SMX ADR could undergo rechallenge with a single oral dose (TMP-SMX; 160mg-800mg OR 80mg-400mg)[9]. This study was approved by the Austin Human Research Ethics Committee (LNR17/Austin/312).

Results:

Twenty-six patients received dapsone PJP prophylaxis during the study period, with 24 meeting inclusion/exclusion criteria. The median age was 59 (IQR 49,69) years, the majority male (54%), and 9 (38%), 8 (33%) and 3 (13%) were receiving PJP prophylaxis for allogeneic HSCT, high-dose corticosteroid therapy, and autologous HSCT respectively. Remaining indications for PJP prophylaxis included receipt of ALL chemotherapy (1, 4%), or cladribine therapy (1, 4%), low lymphocyte CD4 count (1, 4%), and secondary prophylaxis for prior PJP infection (1, 4%). Dapsone 100mg daily was prescribed in the majority of cases (23, 96%), with one patient receiving the combination of dapsone

50mg daily plus weekly pyrimethamine for concurrent toxoplasmosis prophylaxis. Patients received dapsone for a median (IQR) of 67 days (30, 175). Only 42% (10/24) had G6PD assay performed, with none found to be deficient. No cases of breakthrough PJP infection were diagnosed during the study period.

Sixteen patients (67%) were initiated on dapsone PJP prophylaxis to avoid the perceived risk of further myelosuppression with TMP-SMX. Five patients (21%) had a history of mild delayed immune-mediated allergy (Type-B ADR) to TMP-SMX. None experienced rash with dapsone therapy, and one patient was later successfully rechallenged with TMP-SMX without rash recurrence. Three patients (13%) had documented other intolerances to TMP-SMX (Type-A ADR) including hyperkalaemia and nausea. Of the 24 patients receiving dapsone, 6 (25%) were rechallenged on TMP-SMX during the study period, all successfully.

Four (17%) patients, 3 female and 1 male, were identified with confirmed oxidative haemolysis during dapsone therapy. The onset of haemolysis was detected after a median (IQR) of 48 (33, 64) days. Haemoglobin (Hb) changes from baseline are summarised in **Table 1**. Although the median (IQR) Hb level did not change from baseline compared to during dapsone therapy for the whole cohort, (95 [86,106] vs 95 [88,108]; P = 0.69), the patients with dapsone-related haemolysis had reductions in Hb during dapsone therapy (19 to 27%). Two of these patients had a substantial increase in their transfusion requirements attributable to haemolysis occurring concomitantly with their pre-existing bone marrow failure. Only 1 out of 4 had G6PD assay performed, which was normal. All of these patients subsequently ceased dapsone and 2 underwent TMP-SMX rechallenge without subsequent ADR. The remaining 2 patients were assessed as not requiring ongoing PJP prophylaxis.

Discussion:

Whilst limited by a short follow-up period and small patient numbers, we observed no episodes of PJP infection with dapsone in our cohort of patients with haematological conditions, including post-HSCT. A lack of immune-mediated ADR cross-reactivity in those with reported prior sulphonamide ADR was also noted, reduced significantly from the up to 20% previously reported in HIV populations[3-5]. Although the reported incidence of dapsone-induced haematological toxicities is approximately 4% in HIV patients[3], this is likely underestimated due to the ability of normal marrow to compensate for haemolysis. In those with compromised bone marrow function, such as HSCT recipients, up to 20-fold higher rates have been reported and may occur despite normal G6PD activity[10]. We observed a small but significant number of patients with dapsone-related oxidative haemolysis within the first 1-2 months, leading to the risk and expense of potentially avoidable

blood transfusions. A higher reported incidence in other transplant cohorts, too, has resulted in greater hospitalisation and transfusion requirements[11].

G6PD deficiency is estimated to affect 400 million people worldwide and most commonly affects African, Asian, Mediterranean and Middle Eastern ethnicities[12]. In Australia, the only available data are limited to a cohort of southern European decent, reporting a 2.9% incidence of G6PD deficiency[13]. We observed suboptimal G6PD screening in our dapsone patient cohort, with less than half undergoing documented testing during dapsone therapy. Although it is unclear from retrospective review of the clinical notes, we postulate that testing may have been avoided by some clinicians due to G6PD not being an absolute predictor for haemolysis in haematology patients. Nonetheless, low uptake of screening makes it difficult to determine the contribution of G6PD deficiency to oxidative haemolysis observed in our patients, and whether cases could have been avoided.

In our patient cohort, dapsone 100mg per day dosing was utilised in accordance with Australian and European PJP prophylaxis guidelines in patients with haematology malignancies[1, 2]. Although dose reductions or intermittent dose regimens may be employed with dapsone in order to mitigate haematological toxicities [14], a higher incidence of breakthrough PJP infection has been previously noted in HSCT recipients utilising lower dapsone dosing[15], suggesting dapsone dose reductions may compromise efficacy.

The avoidance of TMP-SMX for reasons of myelosuppression also appears unfounded, as rates of leukopenia in solid organ transplant cohorts when TMP-SMX is employed as prophylaxis have been reported at less than 2%[16, 17]. Modern studies have suggested that TMP-SMX therapy when employed as prophylaxis in haematological malignancy does not impact on the degree or duration of neutropenia[18]. A recent Cochrane review of PJP prophylaxis in the non-HIV setting found no difference in adverse events requiring discontinuation when comparing TMP-SMX to no treatment or placebo[19]. Therefore, for those with mild delayed TMP-SMX allergy, TMP-SMX rechallenge or desensitisation should be considered in the peri-transplant period or at commencement of induction chemotherapy, as an alternative to dapsone in accordance with previously published protocols[9].

This study highlights that although dapsone is an alternative agent in PJP prophylaxis, it requires careful monitoring of oxidative haemolysis, irrespective of G6PD status. Deployment of dapsone at the first instance may be avoided in the majority of cases via rechallenge with the first-line agent, TMP-SMX, especially in the peri-transplant period.

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Table 1: Dapsone patient demographics and course observations

Patient	Gender	Haematological condition	PJP prophylaxis indication	Reason for avoiding TMP-SMX	Dapsone daily dose	Dapsone duration (days)	G6PD	Hb baseline (g/L)	Hb during dapsone (g/L)	Haemolysis noted	TMP-SMX rechallenge
1	F	Red cell aplasia	HD corticosteroids	Leukopenia	100mg	34	NA	100	73	Yes	Success
2	F	AA	AlloSCT	Leukopenia	100mg	71	NA	75	58	Yes	NP
3	F	MM	HD corticosteroids	TMP-SMX Type-B ADR, rash	100mg	28	Normal	116	94	Yes	NP
4	M	MF	HD corticosteroids	Leukopenia	100mg	17	NA	101	82	No	NP
5	M	MM	HD corticosteroids	TMP-SMX Type-A ADR, hyperkalaemia	100mg	444	Normal	141	115	No	NP
6	M	MDS	AlloSCT	TMP-SMX Type-A ADR, nausea	100mg	172	NA	124	104	No	NP
7	F	MM	HD corticosteroids	TMP-SMX Type-B ADR, rash	100mg	42	NA	104	90	No	NP

8	F	Lymphoma	CD4 lymphopenia	Leukopenia	100mg	32	NA	100	87	No	NP
9	F	AML	AlloSCT	Leukopenia	100mg	34	NA	84	79	No	NP
10	F	Lymphoma	AutoSCT	Leukopenia	100mg	12	NA	91	88	No	NP
11	M	ALL	AlloSCT	Leukopenia	100mg	82	Normal	112	111	No	NP
12	M	Lymphoma	AlloSCT	Leukopenia	100mg	182	Normal	93	95	No	NP
13	M	Lymphoma	HD corticosteroids	Leukopenia	100mg	30	Normal	88	92	No	NP
14	M	MM	AlloSCT	TMP-SMX Type-B ADR, rash	100mg	22	NA	91	97	No	Success
15	F	MF	AlloSCT	Leukopenia	50mg^	326	Normal	82	88	No	NP
16	F	MM	AutoSCT	TMP-SMX Type-B ADR, rash	100mg	809	NA	96	104	No	NP
17	M	AML	AlloSCT	TMP-SMX Type-A ADR, nausea	100mg	389	NA	132	151	No	NP
18	M	ALL	ALL chemotherapy	Leukopenia	100mg	8	NA	87	103	No	Success
19	M	MM	AutoSCT	TMP-SMX Type-B ADR,	100mg	117	NA	111	134	No	NP

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20	M	Lymphoma	HD corticosteroids	Leukopenia	100mg	62	NA	71	87	Yes	Success
21	F	MM	HD corticosteroids	Leukopenia	100mg	193	Normal	72	89	No	NP
22	F	Langerhans cell histiocytosis	Cladribine	Leukopenia	100mg	13	Normal	86	107	No	Success
23	M	AML	AlloSCT	Leukopenia	100mg	110	Normal	104	136	No	Success
24	M	Jak2-positive myeloproliferative disorder	Previous PJP	Leukopenia	100mg	81	Normal	74	116	No	NP

^dapsone 50mg daily administered plus weekly pyrimethamine/folinic acid for concurrent toxoplasmosis prophylaxis.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; alloSCT, allogeneic stem cell transplant; AA, aplastic anaemia; autoSCT, autologous stem cell transplant; G6PD, glucose-6-phosphate dehydrogenase; Hb, haemoglobin; HD, high dose; MM, multiple myeloma; MDS, myelodysplastic syndrome; MF, myelofibrosis; NP, not performed; PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

Definitions: Type-A – Non-immune pharmacologically predictable adverse drug reaction (e.g. nausea, vomiting, diarrhoea, mild creatine rise due to competitive tubular excretion); **Type-B** – Immune-mediated adverse drug reaction