Original Article

Utility of para-aminosalicylic acid in drug-resistant tuberculosis: Should it be classified as Group D3 or Group C?

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ABSTRACT

Background: The World Health Organization drug-resistant tuberculosis (DR-TB) 2016 guidelines reclassified para-aminosalicylic acid (PAS) as Group D3 "add-on" drug. We studied our DR-TB data wherein PAS was widely and preferably used as a substitute in the standardized regimen in varied situations and report its utility in DR-TB. **Methodology:** This retrospective observational study enrolled both pulmonary and extrapulmonary DR-TB patients receiving PAS in the programmatic management of DR-TB from March 2012 to June 2013. They were divided into seven subgroups on the basis of indication for PAS substitution in the standardized regimen for DR-TB cases. The clinical profile and outcomes were analyzed. **Results:** PAS was substituted in 250 cases (225 – pulmonary DR-TB and 25 – extrapulmonary DR-TB). PAS was used in (1) pre-extensively drug-resistant TB (XDR-TB) fluoroquinolones (FQs) – 136 (54.4%), (2) XDR-TB – 15 (6%), (3) substitute drug for serious adverse events – 3 (1.2%), (4) pregnant DR-TB patients – 5 (2%), (5) patients on successful private-based second-line therapy adopted under the Revised National Tuberculosis Control Program – 10 (4%), (6) substitute drug for previous FQ exposure – 5 (2%), and (7) Category V – 76 (30.4%). Although 51.2% had an unfavorable response (UFR) against 48.8% with FR, wide disparity was noted in subgroups. FR was observed in 68.4% pre-XDR-TB (FQ), 80% pregnant patients, 90% adopted from private on successful second-line therapy, 80% previous FQ exposure against 40% XDR-TB, 7.9% Category V, and 0% PAS substitution for adverse drug reactions (ADRs). UFR was seen in 31.6% pre-XDR-TB (FQ), 20% pregnant patients, 10% adopted from private on successful second-line therapy, 20% of previous FQ exposure against 60% XDR-TB, 92.1% Category V, and 100% on PAS substitution for ADR. **Conclusion:** In view of the safety and efficacy of PAS in our DR-TB patients except for XDR and Category V group, we recommend larger studies with PAS and consider its reclassification into Group C rather than Group D3.

KEY WORDS: Category V, extensively drug-resistant tuberculosis, para-aminosalicylic acid, pre-extensively drug-resistant tuberculosis

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INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is managed as per the Revised National Tuberculosis Control Program (RNTCP) programmatic management of DR-TB (PMDT) guidelines in consensus with the World Health Organization (WHO) DR-TB guidelines. The RNTCP PMDT guidelines were published in May 2012[1] following the WHO DR-TB 2011[2] guidelines. In 2016, a preliminary update of the

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RNTCP PMDT guidelines[3] was available with the start of conditional access to new drugs (such as bedaquiline). However, it had many gray areas and restricted implementation in view of variable laboratory capacity. The 2017 revision of RNTCP PMDT guidelines[4] took into account the updated WHO DR-TB 2016 guidelines.[5] The WHO DR-TB 2016 guidelines had reclassified drugs into groups on the evidence of updates in literature. The encouraging drug trial results for clofazimine and linezolid have resulted in their escalation/prioritization as Group C "core" second-line drugs. However, the age-old drug, para-aminosalicylic acid (PAS), has been demoted and now reclassified as Group D3 "add-on" drugs. This was done in view of the meta-analysis of individual patient data on treatment success and higher frequency of adverse events.[5,6] We studied our DR-TB data (from 2012 to 2013) wherein PAS was widely and preferably used as a substitute drug in standardized regimens in DR-TB cases in varied situations and report its utility in DR-TB therapy.

METHODOLOGY

This retrospective observational study was conducted with Institutional Ethics Committee permission. We included patients (both pulmonary and extrapulmonary DR-TB) who received PAS as part of their therapy regimen in the study period from March 2012 to June 2013. Our DR-TB center attached to a tertiary care hospital and medical college in Mumbai started in March 2012. The format of the PMDT register remained uniform from March 2012 to June 2013. The format of this register was modified after July 2013. We included patients from March 2012 to June 2013 to have uniformity in the data captured in the PMDT register (electronic as well as hard copy). We followed the PMDT DR-TB 2012 guidelines which were valid in the study period. Patients were referred with diagnosis of DR-TB on basis of line probe assay (LPA)/culture drug susceptibility test (DST) for therapy initiation at our DR-TB center. All patients were evaluated with prerequisites which included a complete hemogram, fasting blood sugar, liver function test, renal function test, HIV, urine routine microscopy, thyroid-stimulating hormone, urine pregnancy test (for women of child-bearing age group), chest X-ray, and psychiatry assessment. When available, second-line LPA/DST for fluoroquinolones (FQs) and second-line injectable (SLI) reports were recorded even though it was not a mandatory prerequisite. Treatment was modified as per PMDT 2012 guidelines. A total of 902 patients of DR-TB (both pulmonary and extrapulmonary) were referred to the DR-TB center for therapy initiation. In the study, we included 250 of the 902 patients (both pulmonary and extrapulmonary DR-TB) who received PAS as part of their therapy regimen. They consisted of a heterogeneous group. The reasons for inclusion of PAS as a part of DR-TB regimen were as follows: (1) Cases of multidrug-resistant-TB (MDR-TB) with additional FQ resistance at baseline (second-line naive). These patients were classified in the pre-extensively drug-resistant TB (XDR-TB) (FQ) group. These patients received a regimen consisting of drugs such as kanamycin, ethionamide, cycloserine, and PAS. (2) Cases of MDR-TB with additional FQ and SLI resistance at baseline. These patients were classified in the XDR-TB group. These patients received a regimen consisting of capreomycin, ethionamide, cycloserine, and PAS. (3) As a substitute drug for serious adverse drug reactions (ADRs) requiring omission of any second-line drugs. They consisted of only three patients reporting kanamycin ototoxicity, wherein kanamycin in the regimen was replaced with PAS. These patients received levofloxacin, ethionamide, and cycloserine as the accompanying drugs in regimen. (4) In pregnant DR-TB patients. All these patients when diagnosed with DR-TB were in the third trimester of pregnancy. They received regimen comprising levofloxacin, ethionamide, cycloserine, and PAS. (5) In patients adopted under the RNTCP program who were receiving PAS as part of ongoing successful private-based second-line therapy. These patients were continued on the successful PAS-containing individualized treatment regimens. (6) As a substitute drug in DR-TB cases with documented exposure to FQ in the past. These patients received regimen consisting of kanamycin, ethionamide, cycloserine, and PAS. (7) As part of Category V regimen given to private- (nonprogram) or program-based second-line/Category IV failures. These patients were classified as Category V patients. They received standardized treatment regimen consisting of capreomycin, high-dose isoniazid, linezolid, clofazimine, PAS, amoxicillin-clavulanic acid, and clarithromycin. The demographic data, clinical details, microbiology reports, first- and second-line DST to FQ, and SLI were noted. The follow-up was recorded in view of clinical, microbiological response and outcome. In pulmonary DR-TB cases, sputum conversion was noted. Comorbidities and ADR were recorded. Statistical analysis of qualitative data was done using percentages, mean, and standard deviation (SD). Quantitative data were analyzed with Chi-square tests and unpaired *t*-test.

RESULTS

A total of 902 patients were referred to the DR-TB center for the initiation of DR-TB therapy. Of them, 250 required substitution with PAS during therapy. The patients consisted of 129 (51.6%) males and 121 (48.4%) females. Of them, 213 (85.2%) were adults and 37 (14.8%) were pediatric patients. They consisted of 225 (90%) pulmonary DR-TB and 25 (10%) extrapulmonary DR-TB cases. The mean age was 28.7 (SD ± 13) years. The mean weight was 44.4 (SD ± 11.4) kg. PAS was used in (1) pre-XDR-TB (FQ) – 136 (54.4%) cases, (2) XDR-TB – 15 (6%) cases, (3) substitute drug for serious ADR requiring omission of any second-line drugs – 3 (1.2%) cases (all for kanamycin ototoxicity), (4) pregnant DR-TB patients – 5 (2%) cases, (5) patients adopted under the RNTCP program who were receiving PAS as part of ongoing successful private-based second-line therapy – 10 (4%) cases, (6) substitute drug

in DR-TB cases with documented exposure to FQ in the past – 5 (2%) cases, and (7) Category V patients – 76 (30.4%) cases. The pre-XDR-TB (FQ) and Category V consisted of majority of the cases, that is, 54.4% and 30.4%, respectively. The distribution and clinical profile of patients receiving PAS are given in Figure 1 and Table 1, respectively. There was no statistical difference in the variation and distribution of the clinical profile in the subgroups.

Comorbidities were observed in 66 (26.4%) cases. Twenty-seven (10.8%) patients had diabetes mellitus. Whereas 3 (1.2%) patients had HIV coinfection. Patients were treated as per May 2012 PMDT treatment guidelines. One hundred and fifty-one (60.4%) patients reported ADR on therapy. They consisted of gastroesophageal reflux disease (GERD) in 75 (30%), psychiatric ADR in 67 (26.8%), hypothyroidism in 20 (8%), arthralgia in 15 (6%), hearing loss in 10 (4%), peripheral neuropathy in 7 (2.8%), tinnitus in 5 (2%), acne in 5 (2%), hepatitis in 3 (1.2%), nephrotoxicity in 2 (0.8%), blurring of vision in 2 (0.08%), stomatitis in 2 (0.8%), and seizures in 2 (0.8%). Follow-up sputum acid-fast bacilli (AFB) culture samples were collected at 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, and 24 months of therapy in pulmonary DR-TB patients. Follow-up sputum AFB culture was documented in 187 (83%) of the 225 pulmonary DR-TB patients. Of them, 113 had sputum AFB culture converted and 74 were persistently sputum AFB culture positive. Of the 113, follow-up sputum AFB culture converted patients; 101 were cured, 5 died, 6 were lost to follow-up, and 1 was transferred out. Of the 74 follow-up sputum AFB culture-positive patients, 47 were failures, 19 died, 5 were lost to follow-up, and 3 were transferred out. Follow-up sputum AFB culture reports were not available in 38 of the 225 pulmonary DR-TB patients of which 25 died before follow-up sputum AFB culture samples could be collected, 9 were lost to follow-up, and 4 were transferred out. The rest 25 of 250 were extrapulmonary DR-TB patients. The details of follow-up sputum status in each group receiving PAS are listed in Table 2. Out of the 113 follow-up sputum AFB culture negative patients; majority i.e. 81(71.7%) belonged to the pre-XDR-TB (FQ) group. Out of the 74 follow-up sputum AFB culture positive patients; 52(70.3%) belonged to the Category V group. This was statistically significant ($P < 0.05$; Chi-square test).

Of the total 250 cases, 96 were cured, 20 treatment completed, 6 cured on shorter regimens, 50 died, 23 were loss to follow-up, 47 failed, and 8 were transferred out with outcome details not available. Cure and treatment completed (also known as treatment success) was classified as a FR seen in 122 (48.8%). Two-thirds of these patients belonged to the pre-XDR-TB (FQ) group. Death, loss to follow-up, failure, and transfer out were classified as an unfavorable response (UFR) seen in 128 (51.2%). Although overall 51.2% of patients had an UFR against 48.8% with FR, there was wide disparity in outcome in the various subgroups. FR was observed in 68.4% of pre-XDR-TB (FQ), 80% of pregnant patients, 90% of those adopted from private on a successful second-line therapy regimen, 80% of previous FQ exposure against 40% of XDR-TB, 7.9% of the Category V patients, and 0% where PAS was substituted for ADR. UFR was seen in only 31.6% of pre-XDR-TB (FQ), 20% of pregnant patients, 10% of those adopted from private on a successful second-line therapy regimen, 20% of previous FQ exposure against 60% of XDR-TB, 92.1% of the Category V patients, and 100% wherein PAS was substituted for ADR. The detailed group-wise division of outcome is given in Table 3 and Figure 1. The difference between FR and UFR among the

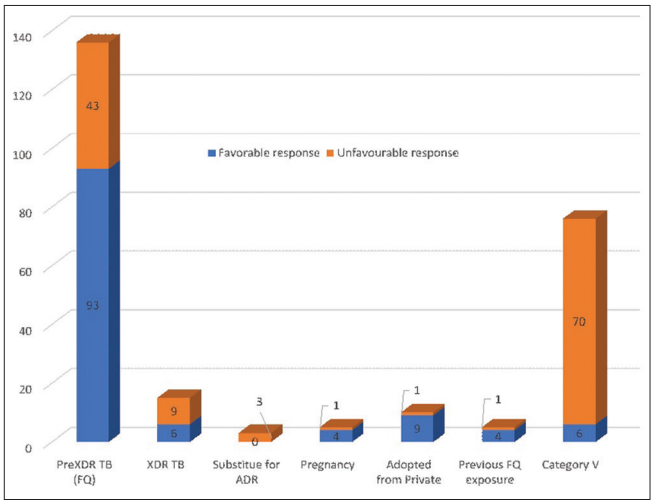

Figure 1: Distribution of patients receiving para-aminosalicylic acid and treatment outcomes. FQ: Fluoroquinolone, Pre-XDR TB (FQ): MDR-TB with additional FQ resistance, XDR-TB: Extensively drug-resistant tuberculosis, ADR: Adverse drug reaction

Table 1: Clinical profile of patients receiving para-aminosalicylic acid

Type of DR-TB patient	Total	Pulmonary/extra-pulmonary DR-TB	Male/female	Adult/pediatric	Mean age (SD)	Mean weight (SD)	DM/HIV	ADR in (*n*) patients
Pre-XDR-TB (FQ)	136	115/21	70/66	116/20	27.3 (12.7)	44.2 (11)	14/1	81
XDR-TB	15	12/3	5/10	12/3	33.8 (15.9)	43 (10)	1/2	10
Substitute for ADR	3	3/0	3/0	3/0	22.3 (1.5)	38.7 (5.5)	0/0	3
Pregnancy	5	5/0	0/5	5/0	25 (1.9)	40.2 (7.8)	0/0	1
Adopted from private on successful regimen	10	9/1	6/4	7/3	26.3 (13.8)	50.1 (17.5)	0/0	5
Previous FQ exposure	5	5/0	3/2	3/2	33.2 (21)	47 (12.8)	2/0	2
Category V	76	76/0	42/34	67/9	30.8 (12.5)	42.8 (11.6)	10/0	50
P		0.1	0.9	0.1	-	-	0.1	0.6

DR-TB: Drug-resistant tuberculosis, DM: Diabetes mellitus, HIV: Human immunodeficiency virus, ADR: Adverse drug reactions, Pre-XDR-TB (FQ): MDR-TB with additional FQ resistance, XDR-TB: Extensively drug-resistant tuberculosis, FQ: Fluoroquinolone

Table 2: Sputum acid-fast bacilli culture status in various groups of patients receiving para-aminosalicylic acid

Type of DR-TB patient	Number of patients	Negative	Positive	Not available	EP DR-TB
Pre-XDR-TB (FQ)	136	81	16	18	21
XDR-TB	15	5	5	2	3
Substitute for ADR	3	0	1	2	0
Pregnancy	5	4	0	1	0
Adopted from private on successful regimen	10	9	0	0	1
Previous FQ exposure	5	4	0	1	0
Category V	76	10	52	14	0
Total	250	113	74	38	25

Unpaired *t*-test; *P* value<0.05. DR-TB: Drug-resistant tuberculosis, EP: Extrapulmonary, ADR: Adverse drug reactions, FQ: Fluoroquinolone, Pre-XDR-TB (FQ): MDR-TB with additional FQ resistance, XDR-TB: Extensively drug-resistant tuberculosis

Table 3: Outcome data of the patients receiving para-aminosalicylic acid

Type of patient	Total cases	Cure	TC	Shorter regimen	Favorable response	Died	Loss to follow-up	Failure	Transfer out	UFR
Pre-XDR-TB (FQ)	136	71	17	5*	93 (68.4%)	21	14	5	3	43
XDR-TB	15	4	2	0	6	4	1	4	0	9
Substitute for ADR	3	0	0	0	0	2	0	1	0	3
Pregnancy	5	4	0	0	4	0	0	0	1	1
Adopted from private on successful regimen	10	7	1	1*	9	0	0	0	1	1
Previous FQ exposure	5	4	0	0	4	0	1	0	0	1
Category V	76	6	0	0	6	23	7	37	3	70
Total	250	96	20	6	122	50	23	47	8	128

*: Shorter regimens consisted of drugs given for a duration of 12-18 months, Chi-square test-*P* value<0.00001. TC: Treatment completed, UFR: Unfavorable response, FQ: Fluoroquinolone, ADR: Adverse drug reaction, Pre-XDR-TB (FQ): MDR-TB with additional FQ resistance, XDR-TB: Extensively drug-resistant tuberculosis

groups was found to be statistically significant (Chi-square test – $P < 0.00001$). Five pre-XDR-TB (FQ) and one patient adopted from private (on successful second-line therapy); totally 6 patients received regimen shorter than 18 months of duration (ranging from 12 to 18 months) as therapy was stopped in view of clinical–microbiological–radiological response and life-threatening ADRs such as psychosis which could not be optimally controlled in spite of maximal medical care.

DISCUSSION

PAS was discovered by Jorgen Lehmann around 1945, about the same time streptomycin was found to be efficacious against mycobacterium TB, although it was accepted 2 years later.[7,8] First reports of therapy with PAS monotherapy were surfaced in 1946.[8,9] The efficacy of PAS and streptomycin was first established in TB in the landmark British Medical Research Council trial.[10] With development of isoniazid, a "triple therapy" containing PAS, isoniazid, and streptomycin became the crux of TB therapy for more than 15 years.[11] Subsequently, ethambutol, rifampicin, and pyrazinamide with isoniazid formed the short-course chemotherapy (SCC) that revolutionized TB therapy.[12] Post-1960s with a decline in cases, research in TB therapy ceased. However, the late 1980s and 1990s witnessed an increase in TB cases with documentation of rifampicin-resistant cases alongside the HIV epidemic. The focus thus shifted on the old drugs again which were re-evaluated for the treatment of DR-TB. PAS, one of such older drugs, along with other drugs such as kanamycin, cycloserine, and ethionamide, was promptly used for the treatment of SCC failures with individual treatment success. Repurposed drugs such as FQ, clofazimine, and linezolid were re-evaluated in DR-TB therapy.[7] However, DR-TB therapy remained capricious with variable outcomes reported globally. Meanwhile, newer drugs in the pipeline such as bedaquiline and delamanid could finish only Phase IIb studies by the current times and were granted accelerated approvals aiming for better treatment outcomes.[4,5]

The previous WHO DR-TB 2011[2] and RNTCP PMDT 2012[1] guidelines outlined PAS as one of the core second-line drugs. Our DR-TB center was established in March 2012 and followed the same for the patients included in the study. With the availability of DR-TB therapy under the programmatic settings and stringent WHO reporting norms, outcome results came into limelight. They highlighted a dismal treatment success of 48% in 2013[13] and 54% in 2017[14] and the need for reforms in the management of DR-TB. With the review of literature from 2011 to 2016, WHO DR-TB 2016 guidelines[5] updated the management in multiple aspects. It included the reclassification of drugs and the same was adopted by the updated RNTCP PMDT 2017[4] guidelines. While the update was based on the analysis of adult individual patient, data formulated were on very low-quality evidence. It opened a new avenue for the new drugs to be utilized in the programmatic settings in spite of only proven efficacy in Phase IIb studies. Most other drugs retained their status or climbed up the ladder. The only drug that was demoted was PAS. This was done in view of the meta-analysis of adult individual patient data suggesting no significant effect on treatment success and higher frequency of adverse events.[5,6] We undertook

this study to analyze our experience with PAS and evaluate our individual patient database to debate the changes suggested in the guidelines.

PAS was utilized at our DR-TB center as a substitute drug most commonly in cases of baseline resistance to FQ and/or SLI, that is, pre-XDR-TB (FQ) – 136 (54.4%) cases and XDR-TB – 15 (6%) cases. We had no cases of pre-XDR-TB (SLI). Both modifications to therapy were made as per the PMDT 2012 guidelines as mentioned in the methodology. Next common reason for patients receiving PAS was as a part of the Category V regimen in program- and private-based second-line therapy failures – 76 (30.4%) cases. Other situations included substitute drug for serious kanamycin toxicity – 3 (1.2%) cases, pregnant DR-TB patients – 5 (2%) cases, patients adopted under the RNTCP program who were receiving PAS as part of ongoing successful private-based second-line therapy – 10 (4%) cases, and substitute drug in DR-TB cases with documented exposure to FQ in the past – 5 (2%) cases. This distribution of high pre-XDR-TB (FQ) and Category V (second-line exposed) patients is consistent with previous reported data from Mumbai. They report a higher than national baseline FQ resistance[15-17] and second-line exposure[18] in the patients referred to the RNTCP DR-TB centers and private-based health-care systems in Mumbai. Sputum AFB culture conversion to negative was seen in 81 (71.7%) cases of pre-XDR-TB (FQ) group. Hence, substitution of PAS at baseline with appropriate rapid/culture DST for FQ was associated with good sputum conversion. This proves the efficacy of PAS when substituted for additional FQ resistance. This was consistent with a previous study from India by Prasad *et al.*, which reported a sputum conversion of 74% on PAS-containing regimen.[19] The study by Kibleur and Veziris has also documented the efficacy of PAS granules,[20] whereas majority, i.e., 52 (70.3%) cases of Category V group remained persistently sputum AFB culture positive. Furthermore, the Category V results are consistent with updated RNTCP guidelines[4] where this regimen is obsolete.

Treatment response of the whole cohort when assessed revealed a FR in 48.8% against UFR in 51.2%. Global DR-TB treatment outcomes under the programmatic settings have been time and again reported by the WHO. Our total treatment success was slightly lower than the 54% treatment success reported by the WHO in 2017 of the patient cohort treated in 2014[14] but consistent with 48% treatment success reported by the WHO in 2013 of the patient cohort treated in 2009.[13] However, there was wide disparity in the outcomes in the various subgroups. While the analysis of outcomes can be debated on in the major subgroups of pre-XDR and Category V, the other smaller subgroups had a good outcome on PAS-based regimens. Exceptions were the XDR subgroup consisting of 15 patients and PAS substitution for ADR consisting of three patients wherein FR was 40% and 0%, respectively. The pre-XDR (FQ) group had a good FR of 68.4% reiterating the need for baseline rapid DST, i.e., second-line LPA in second-line naive patients on diagnosis of DR-TB and prompt substitution of therapy at baseline with PAS. The efficacy of PAS is thus well established in the treatment of pre-XDR-TB (FQ). This group thus may not require newer/repurposed drugs which may be reserved for other complicated cases. Our results in the Category V group stress the need for rigorous follow-up and a need to identify second-line therapy failures program and nonprogram (private) based at the earliest. These patients had the worst treatment success of only 7.9% on the Category V regimen consistent with previous reports from South African researchers in 2006[21] and 2016.[22] In a review article, Donald and Diacon summarize the efficacy and safety of PAS as an important companion drug to be used with newer drugs for DR-TB.[23] Adverse events were noted in 60.4% of patients, major being GERD (30%) and psychiatric adverse events (26.8%), which are attributable to most second-line drugs and did not require stoppage of PAS. Thus, PAS was a safe drug.

Limitations

Our study was limited to a single DR-TB center draining the western suburbs of Mumbai. A referral bias was unintentional due to the geographic drainage area. We tried to minimize the recollection bias by reviewing the data collected in the PMDT register in a uniform pattern (hard copy and soft copy) over a fixed interval of time. Other medical records of patients, for example, the inpatient hospitalization records were unavailable for all patients; hence, additional clinical details could not be included in the study. Thus, the nature and extent of clinical symptoms, signs, radiology, and its correlation to PAS-containing regimens was beyond the scope of the study.

CONCLUSION

DR-TB management has undergone a sea change over the last decade, from the availability of diagnostics and second-line therapy under the aegis of RNTCP to the rapid upscale of the program nationwide. In the current era, focus has shifted to the use and availability of newer drugs such as bedaquiline in DR-TB which holds great promise. However, with these changing times, we need to revisit the older drugs such as PAS to ascertain their utility in view of proven ancient efficacy and safety profile, such that their role in the treatment of DR-TB is better defined and not denigrated or undersized. In view of the documented safety and efficacy of PAS in our DR-TB patients except for the baseline XDR and Category V group, we would recommend further appraisal of literature on PAS and consider its reclassification into Group C rather than Group D3.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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