CASE REPORT

Case Series of Akurit-4 Associated DRESS

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Summary
We describe nine cases of anti-tuberculosis DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a potentially serious complication of treatment that led to interruption of treatment, systemic corticosteroid usage and the resumption of treatment with different regimens. All patients had skin rash, six out of nine patients with hepatitis, two out of nine patients had acute kidney injury, five out of nine patients died. All-cause mortality is high in our cohort.

Key words: *Akurit-4; Tuberculosis; DRESS*

Introduction
Saltzstein and Ackerman in 1959 described a cutaneous adverse reaction to anticonvulsant drugs that included fever, eosinophilia, lymphadenopathy and sometimes hepatosplenomegaly.[1] It was subsequently defined by Bocquet *et al* as drug rash with eosinophilia and systemic symptoms (DRESS).[2] Currently, the Registry of Severe Cutanenous Adverse Reaction (RegiSCAR) scoring system is the diagnostic criteria that is widely used for drug reaction with eosinophilia and systemic symptoms (DRESS).[3] DRESS is considered one of the severe cutaneous adverse drug reaction(SCAR) with a case fatality rate of 10–20%.[4]

DRESS occurs generally between 2 weeks and 3 months after drug initiation and is characterized by fever, rash and visceral involvement. Its not uncommon that antituberculosis drugs are implicated with DRESS.[5]

In 2012, the Ministry of Health, Malaysia, has launched the third edition of tuberculosis clinical practice guideline to make a Grade A recommendation that prefers fixed-dose combination (FDC) anti tuberculosis drug as the first-line regime for intensive phase treatment for newly diagnosed pulmonary tuberculosis (TB) patient.[6] One of the fixed dose combination (FDC) brands that are currently used in Malaysia

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is Akurit-4, that are proven to be bioequivalent to separate-drug regime which consist of EHRZ [ethambutol(E), isoniazid (H), rifampicin (R), and pyrazinamide (Z)] at the same dose level.[7]
We describe the experience as a dermatology department in a tertiary referral hospital in the management of DRESS syndrome associated with Akurit-4. A retrospective observational study of nine patients with DRESS syndrome related to drugs used in the treatment of TB was conducted at the Hospital Tengku Ampuan Afzan, Kuantan Pahang, Malaysia between 2017 and 2020. The diagnosis of TB was based on clinical findings and/or smear positivity.
The causal relationship between antituberculosis treatment and DRESS was based on history of prior treatment, absence of other medications, the disappearance or improvement of symptoms when treatment was stopped and, in some cases, the recurrence of DRESS when re-administered an anti-tuberculosis drug.

Case Series

There were nine patients with predominantly male (seven patients).

Patient number 1 is a 24-year-old lady G2P1 at 22th week period of gestation. She presented with fever associated with maculopapular rash after 35 days treatment with Akurit-4. She was treated with intravenous hydrocortisone, topical corticosteroid and a total course of 14 weeks of tapering prednisolone. Skin biopsy was performed in this case. She had an initial rechallenged with isoniazid after 8th week of SCAR however was withheld due to increment of her ALT. Subsequently at 6th week post-partum(after 14th week post SCAR) she had uneventful desensitization of full regime EHRZ.

Patient number 2 is a 28-year-old Malay gentleman was diagnosed with pulmonary tuberculosis by district clinic and was started Akurit -4 that develop DRESS at Day 10. After the course of systemic corticosteroid, revision of clinical diagnosis was made by respiratory team as bacterial pneumonia and no reintroduction of anti-tuberculosis drug was made.

Patient number 3 has underlying retroviral disease with pulmonary TB and tuberculous lymphadenitis. She developed DRESS 15 days after starting Akurit-4. After her course of prednisolone, she was lost to follow up. Subsequent tracing from a different healthcare centre was found that she had died from pulmonary related complication.

Patient number 4 has underlying Type 2 Diabetes Mellitus (DM) on oral hypoglycaemic agent (OHA). He had first admission at day 15 for DRESS after starting on Akurit-4. He was discharged well with tapering dose of prednisolone. Subsequently was readmitted for recurrent DRESS after introduction of EHRZ. He had six weeks of eventful and prolong hospitalization, that was complicated with line related methicillin-sensitive *Staphylococcus aureus* bacteraemia with infective endocarditis, uncontrolled diabetes that was complicated by erythroderma secondary to DPP4-inhibitors, and an extended spectrum beta-lactamase (ESBL) line related sepsis. He was eventually succumbed due to multi-organ failure.

Patient number 5 had underlying DM presented with severe transaminitis (with peak ALT 2200 U/L and AST 1600 U/L) presented on day 35 after Akurit-4. He succumbed to death due to fulminant hepatic failure. However no documentation in regard to prior level of liver enzymes after the initial course of anti-tuberculosis treatment.

Patient number 6 was a 46-year-old gentleman with underlying retroviral disease and co-infection Hepatitis C. He was admitted for smear positive PTB which complicated with line related enterococcus bacteraemia. He presented with generalized maculopapular rash at day 16 of Akurit-4. He was given initial course of intravenous hydrocortisone 100 mg three times daily for five days and subsequently 6 weeks of tapering course of oral prednisolone.

Patient number 7 has multiple comorbidities i.e.: DM, Hypertension, Ischemic heart disease (IHD). His onset of DRESS was Day 14 after

Table 1. Clinical features, biochemical abnormalities, treatment and outcome of nine cases with Akurit-4 drug-related DRESS syndrome

No	Age/ Race	Sex	Smoking status	Latency (days)	Fever[1]	Skin Rash[2]	LN[3]	TWBC ($10^3$9/L)[4]	Platelet ($10^3$9/L)[5]	Eosinophil count cells/ µl	ALT/ AST (Unit/L)[6]	Creat[7] (µmol/L)	Other Drugs	Initial Treatment Given; Subsequent Therapy	Anti- TB Drug	Outcome	Cause of Death	Skin Biopsy
1	24/ Malay	F	Never smoked	35	Y	Y	N	8.2	369	1600	487/270	35	Pyridoxine	IV Hydrocortisone, TCS; oral prednisolone	EHRZ	Survived	-	Y
2	28/ Malay	M	Never smoked	10	Y	Y	Y	6.1	208	370	53/46	121	Pyridoxine	IV Hydrocortisone, TCS; oral prednisolone	Not re-introduced	Survived	-	N
3	34/ Malay	F	Never smoked	15	Y	Y	NA	7.0	276	1370	346/490	33	Co-trimoxazole	IV Hydrocortisone, TCS; oral prednisolone	NA	Death	TB	N
4	41/ Malay	M	Smoker	15	N	Y	N	22	231	11580	101/249	74	Pyridoxine	IV Hydrocortisone, TCS; oral prednisolone	EHRZ	Death	Sepsis	N
5	46/ Malay	M	Smoker	35	Y	Y	Y	45	400	4600	2200/ 1600	71	Metformin, Pyridoxine	IV Hydrocortisone, TCS; oral prednisolone	Not re-introduced	Death	Liver failure	N
6	46/ Indian	M	Ex-smoker	16	Y	Y	Y	7.2	252	2500	19/NA	138	Vancomycin, Syrup Nystatin	IV Hydrocortisone, TCS; oral prednisolone	SHEL	Survived	-	N
7	60/ Chinese	M	NA	14	Y	Y	NA	11.3	138	100	617/376	82	Nil	IV Hydrocortisone, TCS; oral prednisolone	HREL	Death	Liver failure	N
8	63/ Chinese	M	Ex-smoker	14	N	Y	N	7.7	308	1000	374/NA	NA	Nil	IV Hydrocortisone, TCS; oral prednisolone	Et/Cyclo/L/ Linezolid	Death	COPD	Y
9	75/ Malay	M	Ex-smoker	21	Y	Y	NA	2.2	129	1800	9/NA	79	Nil	IV Hydrocortisone; oral prednisolone	E/H/Cyclo/ Clofazimine	Survived	-	N

F: Female, M: Male, Y: Yes, N: No, IV: intravenous, NA: Not available, TWBC: Total white blood cells, Creat: creatinine, COPD: Chronic pulmonary obstructive disease, TCS: Topical corticosteroids, TB: Tuberculosis, E: Ethambutol, H:Isoniazid, R: rifampicin, Z: Pyrazinamide, S: Streptomycin, Et: Ethionamide, Cyclo: Cycloserine.
[1]Temperature more than 38°C at presentation; [2]maculopapular rash; [3]lymphadenopathies at two or more site; [4]Normal range: 4.0 to 10.0 ($10^3$9/L); [5]Normal range: 150 to 400 ($10^3$9/L); [6]Normal range <50 Unit/L; [7]Normal range: 59 to 104 µmol/L

starting Akurit-4. Six weeks after, he had received a desensitization regime of HREL with recurrent of DRESS syndrome. Unfortunately, he succumbed due to fulminant hepatic failure.

Patient number 8 with underlying ischemic heart disease (IHD) and Chronic Obstructive Pulmonary Disease (COPD) had initial DRESS secondary to Akurit-4 at day 13 of starting treatment. Throughout his course of desensitization regime with different anti-TB he had multiple admission due to various reasons (recurrent DRESS; rash; acute exacerbation of COPD; gastrointestinal-related side effect}. He eventually was on anti-TB regime consist of Ethionamide 500mg OM, 250mg ON, Cyclcoserine 250mg BD, Linezolid 600mg OD, Levofloxacin 500mg OD for a period of five months before died due to anemia and pulmonary related complication.

Patient number 9 had an initial DRESS secondary to Akurit-4 at day 21 of treatment. He had received different desensitization regime that has resulted in recurring of DRESS. Eventually he was able to tolerate his final regime of Isoniazid 200mg OD, Ethambutol 800mg OD, Cycloserine 260mg BD, Clofazimine 100mg OD.

It was difficult to establish a causal relationship between which one or more anti-tuberculosis drugs and DRESS syndrome in these nine cases. As all of these data were collected retrospectively by manual method, some of which had incomplete information. None of the patients undergone laboratory testing of cardiovascular marker (such as creatine kinase (CK) or troponin) or pancreatic enzyme marker (such as amylase or lipase). The clinical information and outcomes are summarised in Table 1.

Discussion

All antituberculosis drugs pose a risk of DRESS syndrome. In general, rifampicin was the most commonly suspected drug because of its larger indications, but in the case of tuberculosis infections, isoniazid was the most commonly suspected drug.[8]

In our case series, the characteristics of antituberculosis drug-associated DRESS syndrome are consistent with literature data[9] with a mean time to onset of 19.4 days. Liver and kidneys were the most frequently involved organs. Skin biopsy were performed in two cases.

A reintroduction of culprit drugs is generally considered contraindicated after a diagnosis of DRESS syndrome. Because of the severity of the tuberculosis infection, the lack of therapeutic options and the risk/benefit balance, a reintroduction could be justified.[10]

Treatment of DRESS syndrome generally includes withdrawal of the offending drugs, correction of electrolyte imbalance, and administration of corticosteroid. In our clinical practice, systemic corticosteroids have become a mainstay of therapy in the form of intravenous hydrocortisone and prednisolone. The prednisolone dose will be tapered down slowly over course of 8 to 12 weeks as rapid tapering may increase the risk of relapse.[9]

Other options include intravenous immunoglobulin or plasmapheresis have been reported to show a promising treatment effectiveness.[11] As none of our patients received this treatment, further studies are required to establish the benefits of these immunosuppressants.

Based on the larger cohort from Taiwan which include a total of 60 cases, DRESS syndrome has mortality rate of around 10%.[4] Among those describe, only two patients on anti-tuberculosis drug and none of them died. In our cohort, five out of nine patients had died due to various reasons (55% mortality rate). This include two patients (22.2%) which attributed directly to fulminant hepatic failure due to DRESS, while the others due do various complication of prolonged hospitalization and comorbidities.

Despite DRESS is a life-threatening syndrome, difficulty in identifying predictive factors for death remain a challenge. It is worth mentioning that five out of six patients with transaminitis died, however whether its usefulness as a marker remain questionable.[11] Apart from that, differences of other clinical variables were not found between cases resulting in death and those that survived.

Blood eosinophilia could be a useful marker of disease progression and treatment response and recurrence in patients with DRESS.[3] However, more experience and clinical evidence is needed.

Existing human leucocyte antigen (HLA) data is minimal in relation to anti-TB drugs. There has been an association reported in Korean patients with DRESS for the class I allele HLA-C*04:01,[12] which extends to the haplotype HLA-A* 11:01-B*15:01-C*04:01. However, these alleles are not reported in the cases presented by Ye et al.[13]

Our study has several limitations. The retrospective review is subject to publication bias. The conclusions we were able to draw are limited by data gaps in these cases. Some details on clinical and outcome parameters or on therapy were often not described. No HHV-6 serology was done due to unavailability of the test in our centre.

Conclusion

Our case series highlights the diagnosis and challenges in clinical management of Akurit-4 associated DRESS and its high all-cause mortality.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclosed.

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References

1. Saltzstein SL, Ackerman LV. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically pathologically malignant lymphomas. Cancer 1959;12:164-82.
2. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15:250-7.
3. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156:609-11.
4. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146(12):1373-9.
5. Kaswala DH. Drug rash with eosinophilia and systemic symptoms syndrome due to anti-TB medication. J Family Med Prim Care 2013;2:83-5.
6. Malaysia Heath Technology Assessment Section (MaHTAS). Clinical practice guidelines on management of tuberculosis. 3rd edition 2012.
7. Lai JML, Yang SL, Avoi R. Treating more with less: effectiveness and event outcomes of antituberculosis fixed-dose combination drug versus separate-drug formulation (Ethambutol, Isoniazid, Rifampicin and Pyrazinamide) for pulmonary tuberculosis patients in real-world clinical practice. J Glob Infect Dis 2019; 11(1): p. 2-6.
8. Allouchery M, Logerot S, Cottin J, Pralong P, Villier C, Ben Saïd B. French pharmacovigilance centers network and the French investigators for skin adverse reactions to drugs. antituberculosis drug-associated DRESS: A case series. J Allergy Clin Immunol Pract 2018;6:1373-80.
9. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L et al. The DRESS syndrome: A literature review. Am J Med 2011;124:588-97.
10. Wang L, Li LF. Difficult clinical management of antituberculosis DRESS syndrome complicated by MRSA infection: A case report. Medicine (Baltimore) 2017;96:e6346.
11. Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol. 2009;145:67-72.
12. Cho YT, Chu CY. Treatments for severe cutaneous adverse reactions. J Immunol Res 2017;2017:1503709.
13. Pavlos R, Redwood A, Phillips E. AdDRESSing T-cell responses to antituberculous drugs. Br J Dermatol 2017;176:292-3.
14. Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ et al. Drug-specific CD4+ T cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. Br J Dermatol 2017;176:378-86.