Title

Cutaneous adverse drug reactions to anti-tuberculosis therapy: an issue for fixed-dose combination treatments?

Running Title

Cutaneous adverse reactions to TB therapy

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Declaration of Competing Interest
None

Dear Editor,

Effective anti-Tuberculosis treatment (ATT) for drug-sensitive Tuberculosis disease (TB) requires a combination of drugs taken for several months. This is a large pill-burden for patients, and fixed-dose combination (FDC) preparations containing first-line ATT enable simpler procurement, prescribing, and reduced number of pills. A systematic review considered FDCs for TB as effective as single drugs used together in combination regimens [1]; however another expert review highlighted concerns, in particular, relating to the pharmacokinetic variability of rifampicin with FDCs, and inadequate quality monitoring [2]. Similar issues have also been noted with non-TB drugs and include manufacturing defects and falsification – all of which emphasises the need for ongoing pharmacovigilance in particular when drugs appear in new formulations [3].

Adverse drug reactions are a concern for patients on ATT, and have clinical and economic consequences, in addition to a negative patient experience [4]. Cutaneous adverse drug reactions (CADR) with ATT range from mild flushing, rash, and itch, through to less frequent severe reactions including Stevens-Johnson syndrome (SJS), generalised hypersensitivity reactions, and drug reaction with eosinophilia and systemic symptoms (DRESS) [5-7]. ATT-related CADR has been reported as affecting 4% of Canadian patients [8], 6% in a Malaysian TB service [9], and a recent Korean cohort identified either SJS or DRESS in 7% [6]. CADR may be more common in TB/HIV co-infected patients, with significant CADR occurring in 13% compared to 8% of HIV negative TB patients in a London cohort [10]. Any first-line drug may be responsible, with studies citing reactions to pyrazinamide [8, 9], rifampicin [6] and ethambutol [11] as a frequent cause.

We noted that several patients treated at our TB centre developed clinically-significant CADR (requiring investigations and treatment interruption, or addition of adjunct medication) shortly after starting the FDC Voractiv (combination Rifampicin, Isoniazid, Pyrazinamide, Ethambutol).

We conducted a retrospective study of all cases of TB disease (both pulmonary and extra pulmonary), believed to be drug-susceptible, starting first-line (4 drug) ATT between January 2016 to February 2021. This research was conducted using information collected by staff within the usual care team as part of routine care (without an intention to use it for research at the time of collection), as such it did not require formal ethics approval under current guidance from the Health Research Authority, UK. Patients were categorised by regimen: Voractiv only; Rifater (combination Rifampicin, Isoniazid, Pyrazinamide FDC) plus Ethambutol (E); and Rifinah (combination Rifampicin, Isoniazid FDC) plus Pyrazinamide (Z) and Ethambutol. Records were examined for history of clinically-significant rash in the first two months of treatment. Data were analysed using chi-squared tests to examine for association between CADR and ATT regimen.

378 patients were assessed. Median age was 39 years, 44% were female. Pulmonary disease occurred in 190 (50%), HIV/TB coinfection accounted for 16 or 4.2% of cases. Main ethnic groups were Asian (41%), Black

(28%), White (26%), Other (5%). Clinically-significant CADR within two months of commencing ATT occurred in 5.3% of patients, and this did not differ significantly between the three FDC groups – *see Table 1.* However, patients treated with Voractiv were more likely to have a rapid onset (less than an hour after first dose) reaction if CADR occurred – present in 4 or 67% of CADR cases who had received Voractiv, compared to 1 or 12.5% of CADR using Rifater+ Ethambutol (RR 5.3, 95% CI 0.8 – 36.3, *p= .036*). Rapid-onset CADR was not seen in the 125 patients treated initially with Rifinah, Pyrazinamide and Ethambutol - *see Table 1*. Due to small numbers, it is unclear if differences between the three groups were due to ATT regimen or other differences between the groups. No CADR occurred in the 16 cases with HIV/TB co-infection. None of the patients with rapid-onset rash had a history of previous exposure to ATT; two patients who experienced non-rapid rash had taken ATT in the past – one from the Voractiv group and another from the Rifinah+Z+E group.

Investigation of CADR by the treating team varied. Five of nine (55%) CADR cases who had a full blood count measured had eosinophilia (>500 cells/microlitre), the other 11 had no results recorded. Four of 13 (31%) in whom liver function tests were measured had a hepatic transaminitis; in 7 patients no results were recorded.

In 11 of 15, a suspected causative drug was omitted subsequently: Pyrazinamide (in 5), Isoniazid (3), Rifampicin (2), Ethambutol (1) - and all successfully completed ATT. Four continued without initial ATT interruption, mainly using oral antihistamines and occasionally topical steroids; one had no intervention documented. In most patients, omission of a drug resulted in treatment being extended.

As described elsewhere, CADR is common and affects around one in twenty people taking ATT; our data suggest that the frequency of CADR is similar between different FDCs, though Voractiv may be associated with more rapid-onset CADR (within an hour of first dose). Larger studies are required to confirm this, and to explore the mechanism of this reaction. This includes the possibility that the rapid-onset rash (which appeared to occur over a discrete time-scale and at one TB centre) may have been specific to a batch of Voractiv. These cases have been reported to the UK MHRA YellowCard system for reporting adverse events.

Approaches to managing ATT-related CADR are outlined in several guidelines; however in practice this is often not standardised [12]. Severe CADR may require treatment interruption and drug rechallenge, de-sensitisation, or exclusion of potential causative drugs [12]. Due to the limited options available to treat TB effectively and safely, the benefit of rechallenge may outweigh the risk [12].

We found there to be a lack of standardised management for patients experiencing ATT-associated CADR. This impaired our ability to detect systemic events such as liver injury, and highlights the importance of a structured approach to managing adverse reactions during ATT. A new rash, when taking ATT, should prompt blood tests to identify possible causes and exclude associated drug-induced liver injury. Local practice guidance is now in place at our service to optimise the management of ATT-associated CADR.

Although this was a small, single-centre retrospective study, which is therefore likely to be underpowered to explore fully the relationship between patient characteristics and frequency of CADR, we believe our report highlights several clinically-important issues concerning ATT cutaneous drug reactions and their management.

When FDCs for TB were globally endorsed in 1999, continuous surveillance was recommended [13], however current efforts appear insufficient [2]. Our study emphasises the need for ongoing monitoring of FDCs, despite the individual drugs being in use for decades. Heightened surveillance or a larger cohort study could investigate the potential early-onset effect of Voractiv further. This is important as data from randomised drug trials may not reflect the true prevalence of CADR, or allow comparisons between the different FDCs used in clinical practice.

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Declaration of Competing Interest

None

Contributors

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Table 1: Frequency of clinically significant cutaneous adverse drug reaction (CADR) within two months of commencing treatment, by anti-tuberculosis therapy (ATT) regimen (January 2016 - March 2021)

ATT regimen	Patients n	CADR requiring intervention n (%)	Rapid onset (≤ 1 hour) n (% of CADR cases)
Voractiv	110	6 (5.5)	4 (67)
Rifater+E	143	8 (5.6)	1 (12.5)
Rifinah+Z+E	125	6 (4.8)	0

Total	378	20 (5.3)	5 (25)