Pharmacovigilance of new TB drugs

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What is pharmacovigilance?

“science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.”

The importance of pharmacovigilance, WHO, 2002
Why to do pharmacovigilance?

What is its intrinsic value?

- Adverse drug reactions (ADRs) can lead to
  - reduced quality of life
  - interrupting treatment
  - avoidable morbidity
  - treatment failure
  - death
Why to do pharmacovigilance?
What is its intrinsic value?

Pharmacovigilance is essential for patient-centred care and proper clinical management.
Why to do pharmacovigilance?
What are the consequences of doing it or not?

• Keep in mind that:
  – Burden of adverse drug reactions informs planning
  – Clinical trials provide only limited information
  – Every country is different
  – Public confidence has implications in public health interventions
Why to do pharmacovigilance in tuberculosis if…?

- Anti-TB drugs are well-established medicines?
- All reactions are well documented over decades?
Pharmacovigilance and tuberculosis: applying the lessons of thioacetazone

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Following its introduction in the late 1940s, thioacetazone was widely-used as an anti-tuberculosis medicine in the following decades.1 Reports of cutaneous hypersensitivity reactions related to its use emerged in the literature soon after its introduction and by the early 1970s the association between the medicine and the adverse drug reaction was well established.1,2 Despite the increased recognition of this risk, thioacetazone remained in use mainly in low-income countries because of its low cost.3

In the late 1980s and early 1990s, reports appeared from Africa describing an increased risk of severe cutaneous reactions associated with the use of thioacetazone in persons with human immunodeficiency virus (HIV) infection.4,5 At that time, HIV infection had already reached epidemic proportions in many African countries. Among children and adults with HIV infection and tuberculosis, high fatality was observed in those who developed Stevens-Johnson syndrome or toxic epidermal necrolysis when treated with regimens containing thioacetazone.4,5 In 1991, the World Health Organization (WHO) recommended replacing thioacetazone with ethambutol in patients with known or suspected HIV infection.6 Thioacetazone is no longer included in WHO’s recommended first line treatment for tuberculosis and is now reserved for uncommon situations in which treatment options have been compromised by resistance to other anti-tuberculosis medicines in HIV-negative individuals.7

For more than 50 years, WHO has been encouraging countries to reinforce their pharmacovigilance – the surveillance of adverse drug reactions – at national level.7 Nonetheless, under-reporting is a major problem, both in developed and developing countries. Computing adverse drug reaction frequencies for a particular medicine is impossible without spontaneous reporting, as there is no way to obtain a denominator – an accurate estimate of the number of people exposed to the drug. Moreover, incomplete reports mean that it is difficult to establish a relationship between the suspected medicine and the adverse drug reaction.

Currently the WHO Programme for International Drug Monitoring – a worldwide pharmacovigilance network – receives individual case safety reports from the national drug safety authorities of 118 countries. Spontaneous reports of adverse drug reactions, submitted by participating countries are gathered in the database Vigibase™, which is maintained by the WHO Collaborating Centre, the Uppsala Monitoring Centre in Sweden.8 Vigibase has accumulated over nine million individual case safety reports since the late 1960s, over half of which have been received in the last five years. This reflects an improved regulatory environment, greater awareness of the need for drug safety monitoring, and the expansion of the WHO Programme for International Drug Monitoring. Vigibase currently accrues about 800,000 individual case safety reports each year.9

We searched Vigibase for adverse drug reactions related to thioacetazone and found an increase in reports of skin conditions, some of them reported as severe, in Thailand during the 1980s and early 1990s (Fig. 1). These reports are consistent with – and even predate – the publications from Africa. While there is no information about whether these conditions were occurring in people with HIV infection, it is notable that the timing of the reporting peak coincides with the evolution of the HIV epidemic in Thailand.10 Isolated reports of cutaneous hypersensitivity were reported by other countries during this time but no other country reported as large an increase as Thailand.

The lessons learnt from the thioacetazone episode remain pertinent today; medicines that have been in use for a long time need to be monitored for safety when used for new indications or in a population with different comorbidity profiles. The spontaneous reports from Thailand show the usefulness of databases for pharmacovigilance despite the limitations of these reports.

The treatment of drug-resistant tuberculosis is now poised to undergo changes. More patients in more countries will be receiving treatment in the coming years and important modifications in the regimen composition and duration will be increasingly introduced. Current treatment regimens for these patients are long and complex and their toxicity when used in certain patient

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Why to do pharmacovigilance in tuberculosis?
What is its intrinsic value?

Pharmacovigilance is essential for TB patient-centred care and proper TB clinical management.
Why to do TB pharmacovigilance? What are the consequences of doing it or not?

- Keep in mind the increasing demand on products for off-label use in MDR-TB management.
Why to do TB pharmacovigilance? What are the consequences of doing it or not?

- Keep in mind the WHO policy on the use of shorter-treatment regimens for MDR-TB:
  - To be delivered under operational research conditions to assess effectiveness and safety, after approval of national ethics review committee.
Why to do TB pharmacovigilance? What are the consequences of doing it or not?

- Keep in mind that compassionate use programmes will become more widely used due to:
  - XDR-TB
  - Some countries may not approve drugs until full development of the compound
Why to do TB pharmacovigilance?
What are the consequences of doing it or not?

- Keep in mind that public confidence is based on credibility, among other factors.
Why to do TB pharmacovigilance? What are the consequences of doing it or not?

- Keep in mind that drug safety is a big issue in new TB drugs:
  - conditional approval
  - drug to drug interactions
Why to do TB pharmacovigilance?
What are the consequences of doing it or not?

- Off-label use in MDR-TB management
- Shorter regimens for MDR-TB
- Compassionate use
- Introducing new TB medicines
- Planning/budgeting TB control
- Public confidence/ NTP credibility
Feasibility of doing Pv in TB control

- In 2012, WHO produced the very first handbook on pharmacovigilance for TB!
Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative

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SUMMARY

Adverse events associated with second-line drugs have been mentioned as obstacles in the management of multidrug-resistant tuberculosis (MDR-TB). Data on adverse events were collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast). The results show that among 818 patients enrolled on MDR-TB treatment only 2% of patients stopped treatment, but 30% required removal of the suspected drug(s) from the regimen due to adverse events. The study shows that adverse events are manageable in the treatment of MDR-TB in resource-limited settings provided that standard management strategies are applied.

KEY WORDS: MDR-TB; DOTS-Plus; adverse events; second-line drugs
Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies

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ABSTRACT

Objectives: Given the spread of multidrug-resistant tuberculosis (MDR-TB), new therapies are urgently needed, including the repurposing of existing drugs. We aimed to assess key considerations for the clinical and programmatic use of clofazimine (Cfz), a raminophenazine with antimycobacterial activity currently used to treat leprosy.

Design: Fixed and random effects meta-analysis of cohort studies and systematic review.

Setting: Electronic and manual searches were combined.

Inclusion criteria: Observational studies on treatment of multidrug-resistant and extremely drug-resistant tuberculosis with Cfz or a Cfz-containing regimen, and published guidance and documents relating to cost and availability were included.

Strengths and limitations of this study

- We have reviewed a comprehensive body of peer-reviewed literature and policy guidance relating to the safety, use, cost and availability of clofazimine (Cfz) in clinical practice.
- This study shows that the burden of safety issues associated with Cfz use appears to be manageable by national TB programmes. The widespread use of Cfz is limited by low availability and relatively high cost.
- Few studies were included in the meta-analysis since only a smaller number of studies have been conducted with Cfz. Further research is needed.
Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis

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Although cycloserine (CS) is recommended by the World Health Organization as a second-line agent for the treatment of multidrug-resistant tuberculosis (MDR-TB), safety concerns have impeded its uptake by several national TB programmes. Terizidone (TRD), a structural analogue of cycloserine, may be better tolerated. To assess the safety of CS and TRD for TB treatment, a systematic review and meta-analysis were conducted. From articles published up to December 2011, 27 studies with 2164 patients were included in our review of CS use. The pooled estimate for the frequencies of any adverse drug reaction (ADR) from CS was 9.1% (95% CI 6.4–11.7); it was 5.7% (95% CI 3.7–7.6) for psychiatric ADRs, and 1.1% (95% CI 0.2–2.1) for central nervous system (CNS) related ADRs. TRD showed no better to moderately better safety than CS in a systematic review of the available literature. The published evidence suggests that CS is associated with a higher frequency of psychiatric and CNS-related ADRs than other second-line drugs. While data were limited, treatment discontinuation rates appeared to be manageable. There were no significant differences in tolerability by region, study period or combination. As countries review and revise their treatment programmes, CS, and potentially TRD, should be included in MDR-TB treatment regimens. Adequate information on possible ADRs should be provided to patients, their families and attending health care workers. Greater attention to MDR-TB patients’ mental health and a significant increase in resources devoted to pharmacovigilance and treatment of MDR-TB are essential.

KEYWORDS: cycloserine; terizidone; tuberculosis; drug resistance; adverse drug reactions
WHO Strategy for Collecting Safety Data in Public Health Programmes: Complementing Spontaneous Reporting Systems

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Fig. 1 The relationship between spontaneous reporting, TSR and CEM. All medical incidents (events) that patients experienced while on treatment can be captured by CEM. Those events considered noxious and unintended and suspected to be caused by the medicine are reportable as ADRs through spontaneous reporting. TSR focuses on the collection of information on specific ADRs, with specific medicines, in defined patient groups. ADRs adverse drug reactions, CEM cohort event monitoring, TSR targeted spontaneous reporting
Feasibility of mainstreaming Pv in TB control

- All Global Fund approved programmes using shorter regimens are budgeting the cost of introducing pharmacovigilance in their operational plans.

- Pharmacovigilance is now being included in the budgeting tool developed by the WHO/TME unit, instrumental in the development of National Strategic Plans (needed for access to Global Fund resources).

- TBTEAM roster of consultants in pharmacovigilance is being populated. Please apply if you are an expert and would like to support countries!
Bottomline!

- Patients suffer without treatment
- Treatment should not worsen their suffering, unnecessarily!

Dominic Chavez/WHO