

MADRAC *Bulletin*

For healthcare professionals only

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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.



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DISCLAIMER

The MADRAC Bulletin is published by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. This publication is meant to provide updates on medication safety issues to health care professionals, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss of whatsoever arising from the use or reliance on this publication. The opinions expressed in all articles are the authors' own and do not necessarily reflect the view of NPRA.

We would like to thank the Director General of Health, Malaysia for his permission to publish the signal and case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).¹ The case reports presented in this section are intended to serve as a reminder of potential adverse events that health care providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not exhaustive but rather represents a selection of clinically relevant items that warrants dissemination.

Tacrolimus-Induced Toxic Leukoencephalopathy

By Jeeven Raj Rajagopal

Case Report¹

A 50-year-old male patient with underlying acute-on-chronic alcoholic liver disease underwent cadaveric liver transplantation and was initiated on oral tacrolimus 2 mg twice daily for immunosuppression. The dose was gradually titrated up based on therapeutic drug monitoring (TDM). Eight days later, the patient was discharged with a dose of 4.5 mg twice daily.

After returning home on the day of discharge, the patient developed forgetfulness, lethargy, excessive sleepiness, and was unable to ambulate independently. He presented to the hospital the following day with disorientation to place, though still oriented to person and time. Neurological evaluation and investigations were initiated. By Day 11, his neurological condition deteriorated, progressing to right-sided hemiparesis. A computed tomography (CT) scan conducted the next day revealed an acute infarct in the anterior cerebral artery (ACA) territory, and he was referred to the neuromedical team.

On Day 14, a brain magnetic resonance imaging (MRI) suggested **tacrolimus-induced toxic leukoencephalopathy**, given the recent clinical history of transplantation. The radiological differential diagnoses included posterior reversible encephalopathy syndrome (PRES) and progressive multifocal leukoencephalopathy (PML). There was no MRI evidence of encephalitis or cerebritis.

Tacrolimus was immediately discontinued upon diagnosis, and the patient showed gradual neurological improvement, with return of mild sensation on limbs, and recovery of speech and swallowing. On Day 22, the patient was transferred to a rehabilitation hospital for physiotherapy and supportive care. Given the presence of underlying comorbidities and possible use of concomitant drugs, the drug-reaction causality was assessed as *possible*.

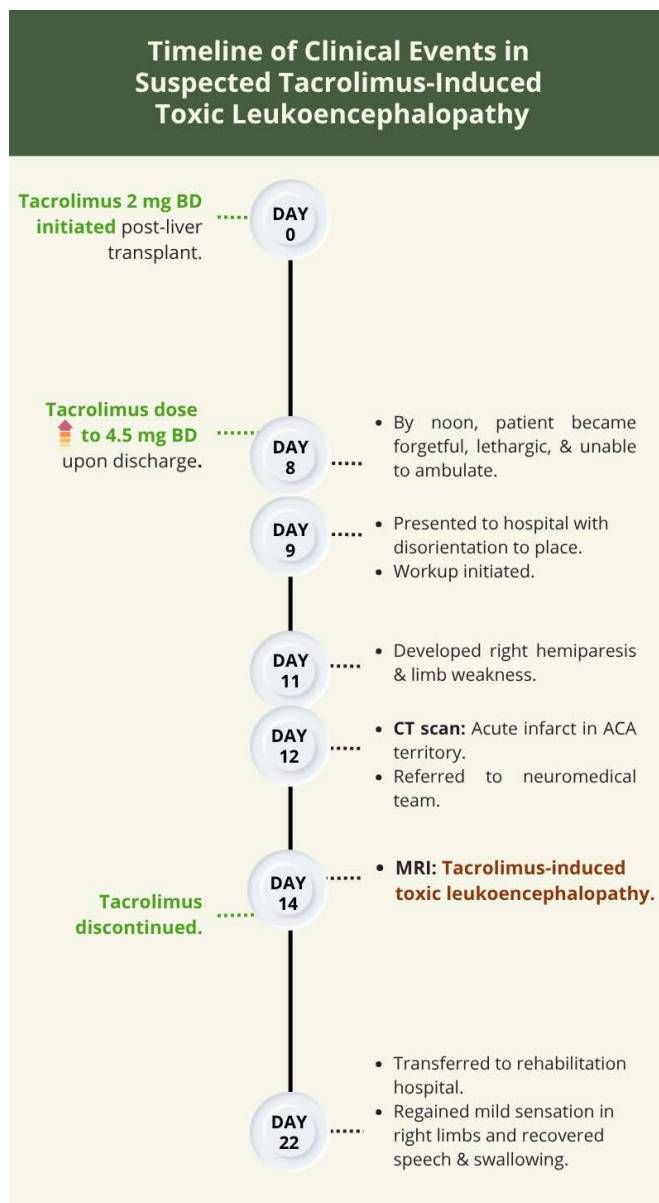


Figure 1. Timeline of Clinical Events in Suspected Tacrolimus-Induced Toxic Leukoencephalopathy

Abbreviations:

ACA: anterior cerebral artery; BD: twice daily;

CT scan: computed tomography scan; MRI: Magnetic resonance imaging

Discussion

Tacrolimus is a macrolide calcineurin inhibitor indicated for primary immunosuppression in liver and kidney allograft recipients as well as liver and kidney allograft rejection resistant to conventional immunosuppressive agents.² Tacrolimus works by binding to the intracellular protein FKBP12 to form a complex that inhibits calcineurin.^{2,3} This inhibition results in the suppression of cytotoxic lymphocytes formation, T-cell activation, T-helper cell-driven B-cell proliferation, lymphokines production, and interleukin-2 receptor expression. There are currently 16 registered products in Malaysia containing tacrolimus as a single active ingredient. Of these, 12 products are registered for oral administration, three for topical use, and one for infusion.⁴

Neurotoxicity is a known adverse effect of tacrolimus, with clinical manifestations ranging from mild symptoms like tremors and headaches to more severe conditions such as encephalopathy and leukoencephalopathy.^{2,3,5-7} **Toxic leukoencephalopathy**, which is characterised by diffuse white matter abnormalities, is a rare but serious complication potentially associated with tacrolimus therapy.^{3,5-7} Early signs may include headaches, dizziness, ataxia, subjective diplopia, and hand tremors. In more severe cases, it may rapidly progress to altered mental status, disorientation, confusion, unresponsiveness, prolonged coma, and in some instances, refractory generalised status epilepticus.

The exact mechanism of tacrolimus-induced neurotoxicity remains unclear but is likely multifactorial.^{3,5} One key proposed mechanism involves tacrolimus's high lipophilicity, which facilitates its passage through the blood-brain barrier, potentially leading to vasogenic oedema, demyelination, and cytotoxic oedema.^{3,5,6} Other contributing factors may include direct endothelial damage, blood-brain barrier disruption due to impaired drug efflux transporters like P-glycoprotein, and direct neurotoxin effects.^{3,6}

The onset of tacrolimus-induced neurotoxicity, including leukoencephalopathy, usually occur within the first month following transplantation and initiation of therapy, but may also arise months or even years later.^{3,5,6} Notably, one case report described leukoencephalopathy developing 10 years after liver transplantation, with gradually progressive symptoms possibly linked to long-term tacrolimus use.⁶

Early recognition of tacrolimus-induced toxic leukoencephalopathy is critical to prevent permanent neurological damage.^{3,6} Neurotoxicity can occur at both therapeutic and elevated tacrolimus levels, highlighting the limited correlation between serum trough levels and neurotoxicity risk.^{3,6,7} Management primarily involves prompt discontinuation of tacrolimus, which often results in clinical and radiological improvement.^{3,5} Dose reduction alone may be inadequate.⁶ Once other possible causes have been excluded, discontinuation of tacrolimus should be considered, since diagnosis of tacrolimus-induced neurotoxicity is typically confirmed by neurological improvement following drug withdrawal.^{3,6} Switching to an alternative immunosuppressive agent may also be considered to prevent graft rejection and recurrence of neurotoxicity.³

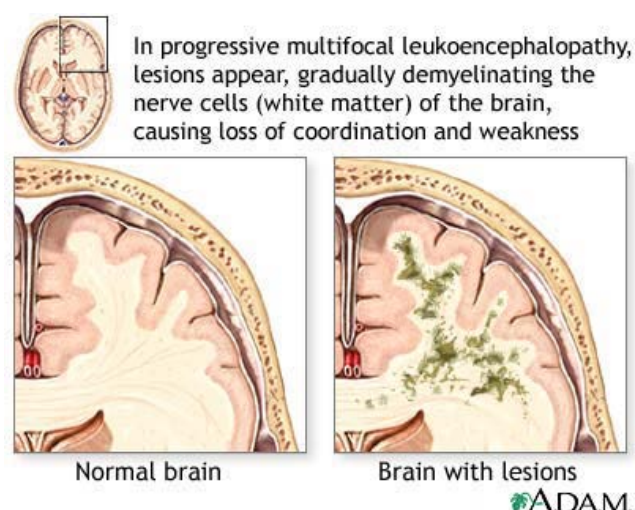


Figure 2. Leukoencephalopathy⁸

As of May 2025, a total of **115 reports involving 181 adverse events** suspected to be related to tacrolimus were reported to the NPRA.¹ The most frequently reported adverse events were tremor (21 reports), diarrhoea (8), and kidney transplant rejection (5). To date, NPRA has received **one local report of toxic leukoencephalopathy**, as described above. According to VigiBase, the WHO global database of individual case safety reports, there have been 17 global cases of toxic leukoencephalopathy and 140 cases of toxic encephalopathy as of 30 May 2025.^{9*}

***DISCLAIMER**

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

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Advice for Health Care Professionals

- **Be vigilant** for the potential risk of neurotoxicity, including toxic leukoencephalopathy, in patients receiving tacrolimus, even when tacrolimus levels are within the therapeutic range.
- **Monitor** patients closely at tacrolimus initiation and during the early post-transplant period. Continue periodic monitoring thereafter, as neurotoxicity may also occur months or years later.
- **Remind** patients to inform healthcare providers that they are taking tacrolimus, as certain concomitant medications such as CYP3A inhibitors (e.g., azole antifungals, macrolides) and prokinetic agents (e.g., metoclopramide) may increase tacrolimus blood levels and neurotoxicity risks. **Advise** patients to avoid alcohol or grapefruit consumption.
- **Educate** patients to seek immediate medical attention if they develop early neurotoxic symptoms suggestive of toxic leukoencephalopathy, such as fine tremors, headaches, or subtle cognitive changes.
- Consider **referral** to a neurology team and **conduct** investigations such as brain MRI if patients present with neurological symptoms.
- If tacrolimus-induced toxic leukoencephalopathy is suspected and other causes have been excluded, consider **discontinuing** tacrolimus, as diagnosis is typically confirmed by neurological improvement following drug withdrawal. Consider **switching** to an alternative immunosuppressive agent if clinically indicated.
- **Report** any adverse events suspected to be related to products containing tacrolimus to the NPRA.

Features

Training

Workshop on Effective Social Media Content Creation

On 9 July 2025, the NPRA Pharmacovigilance Section organised an engaging workshop on effective social media content creation. The training was conducted by Mr. Syed Ilyia Hariz, a senior reporter from the Malaysian National News Agency (BERNAMA).

The first session began with an overview of managing the official social media accounts of a government agency. Mr. Syed Ilyia shared insights on how to leverage various social media platforms to communicate NPRA related information effectively. He highlighted strategies for creating impactful content, focusing on techniques to increase user engagement. A key concept discussed was *hook content*, which is the use of compelling opening elements to immediately capture attention and encourage further interaction with the post.



He also touched on key factors that contribute to trending content, such as timeliness, credibility, public interest, emotional engagement and visual appeal. Towards the end of the first session, Mr. Syed Ilyia provided practical tips on crafting engaging posts, as well as optimising the timing and dissemination of content across different platforms to maximise reach and impact.

The second session involved hands-on training where participants explored an artificial intelligence (AI)-powered tool to generate ideas for creative content. Participants also learnt how to design visually appealing posts using a user-friendly graphic design platform. The workshop concluded with a group activity where participants worked in pairs, applying their newly acquired skills to develop social media content on selected healthcare topics.



We hope that the insights gained from this workshop will empower the NPRA to enhance its social media presence, expand outreach efforts, and develop more engaging content. This aligns with our aim to strengthen communication with the general public.

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts/DCA directives that were recently issued, which are available on the NPRA website.

Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
	Title	Date	
1 Rituximab	Risks of Enteroviral Meningo-encephalitis and False-Negative Serologic Testing of Infections	4-Jul-2025	NPRA.600-1/9/13 (55) Jld. 1 [9-May-2025]

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit www.npra.gov.my
2. Report ADR as **Healthcare Professional**
 - a) Choose **Online Reporting** or
 - b) Download the **ADR manual form** and submit the completed form via email or post:



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To join the mailing list:



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