



Tacrolimus Immunosuppression Causes Drug-Induced Hypersensitivity Reactions in Liver-Transplant Patients: A 3-Case Report

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ABSTRACT

Background. *Drug-induced hypersensitivity reactions attributed to the immunosuppressive agent tacrolimus after an organ transplant are rare in the literature. We present 3 cases of male adult patients grafted with a cadaveric liver who developed delayed hypersensitivity reactions to tacrolimus in the form of the prolonged-release capsules (Advagraf). Furthermore, the appropriate drug concentration solutions used for allergy testing are proposed.*

Methods. All patients received a liver transplant (LT) because of cirrhosis of various etiologies. They were immunosuppressed with tacrolimus once daily. Several months after they had been placed on an immunosuppressive regimen with tacrolimus in the form of prolonged-release capsules (Advagraf), the patients presented with delayed hypersensitivity reactions and torturous pruritic rash that affected the whole body and was unresponsive to treatment with oral ursodeoxycholic acid, cholestyramine, or levocetirizine. Allergy testing that was performed by skin prick testing was negative. Nevertheless, intradermal testing yielded positive results in all 3 patients. Management was by interruption of the culprit agent, which was followed by symptom resolution. The immunosuppressive treatment was continued with alternative drugs.

Results. Appropriate nonirritating drug concentration solutions of the drug used for intradermal testing were highly sensitive and confirmed the clinical diagnosis of tacrolimus allergy in all the affected patients.

Conclusion. Immunosuppressive treatment with tacrolimus in the form of prolonged-release capsules may cause a drug hypersensitivity reaction. A suspicion of allergy warrants a referral for allergy testing. Pruritic rash refractory to treatment in liver transplanted patients should be evaluated by an allergist for possible drug allergy when bile stasis and graft disease have been excluded. Intradermal testing has proven a highly sensitive method for confirming a drug allergy diagnosis, whereas skin prick testing did not.

TACROLIMUS (TAC) is a widely used immunosuppressive regimen in organ transplantation [1]. In the literature, reported cases of allergy to TAC are rare. In 2000, Riley et al [2] published a patient case of a bone marrow-transplanted female adult patient who was allergic to macrolide antibiotics and had cross-reactivity to TAC. Kang et al [3] reported anaphylaxis attributed to castor oil derivatives, which are used as additives to TAC and cyclosporin, in a male adult patient who

received TAC and cyclosporin after a bone marrow transplantation. Here, we report 3 cases of male adult patients who developed post-liver transplant (LT)-delayed hypersensitivity

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reactions to TAC. We regard the report of these 3 cases as innovative not just because allergy cases to TAC are rare but also because a similar clinical presentation of TAC allergy has not been previously reported. Additionally, we propose appropriate drug concentration solutions for allergy testing to TAC, which are not yet recommended in the existing literature.

PATIENTS AND METHODS

The report of cases regarding patients' diagnostic procedures, management, and follow up when anonymized does not require permission or approval by the hospital management board or the science advisory board of the Hippokration Hospital of Thessaloniki, Greece.

The recovered organs (liver) were obtained from deceased donors, and the medical history of the donors concerning allergy is unknown.

The immunosuppressive schedule of the regimen followed in our patients was the following: In all but one patient, immunosuppression in the first postoperative month was with methylprednisolone (MP) (16 mg initial dose, which was weaned off in the following month), mycophenolate mofetil (MMF) (CellCept: 750 mg $\times$ 2) and TAC in the form of the prolonged-release capsules for oral use Advagraf 3 mg once daily. In the ninth postoperative month, the regimen changed to MMF and TAC or TAC alone. In 1 patient (third case), the initial immunosuppressive regimen (MP and MMF) was coadministered with cyclosporine (Neoral: 125 mg $\times$ 2 per os). In postoperative month 13, cyclosporin was replaced by TAC.

The skin test solutions for allergy testing (skin prick tests [SPTs] and intradermal tests [IDTs]) to TAC were prepared by dissolving 1 mg of the drug dry powder extracted from the capsule in 10 mL of diluent (water for injection). This initial solution served as the 1:10 solution (0.1 mg/mL). Further dilutions of 1:100 and 1:1000 were also prepared. IDT to hypromellose was prepared with a solution of 1% in a 1:10 dilution. Sodium croscarmellose and magnesium stearate, being the drug's excipients, were also prepared for testing at a 0.01 mg/mL solution concentration [4].

For patch testing, the patch testing chambers by Chemotechnique Diagnostics (IQ Ultimate, Vellinge, Sweden) were used. Hypromellose (1% ophthalmic solution) was used by placing 1 drop of the solution on a patch test chamber. Croscarmellose sodium and magnesium stearate were used in the form of powder. Normal saline 0.9% was added to the dry ingredient via syringe 1:1 and was subsequently stirred until a paste-like consistency was achieved. The mixture was finally placed into a patch well. The control was left blank. A follow-up appointment was made for evaluation after 72 hours.

Lactose monohydrate, also an excipient, was not tested because there was no history or clinical picture relevant to lactose intolerance in the patients.

Case 1

A 56-year-old male patient with liver cirrhosis due to primary sclerosing cholangitis was managed with orthotopic LT and a Roux-en-Y hepaticojejunostomy.

In postoperative month 30, the patient developed a generalized pruritic rash. Blood bilirubin levels were mildly elevated (3.2 mg/dL and 1.84 mg/dL total and direct bilirubin, respectively), and the bile acid levels were 8.2 μ mol/L (standard value: 0.9-9 μ mol/L). The investigation of the common causes of pruritus in an LT patient and the graft biopsy results for rejection, vascular complication, and bile stasis were all negative. The resistance of pruritus to the treatment with ursodeoxycholic acid (UDCA), cholestyramine, and levocetirizine in combination with

excluding other diagnoses for pruritus and the sporadic report in the literature of drug hypersensitivity reactions to immunosuppression led to the suspicion of possible drug allergy, and further investigation was organized. The patient at this time received MMF (CellCept: 750 mg $\times$ 2 orally) and tacrolimus (Advagraf: 3 mg). SPTs and IDTs to MMF were negative. SPTs to TAC solutions 1:10, 1:100, and 1:1000 were negative compared with the positive control (histamine control test: 5 mm wheal). The IDTs yielded the following results: the 1:1000 test solution was negative, the 1:100 test was positive with a 5 mm wheal, and the 1:10 test was positive with a 5 mm wheal (Fig 1A). The drug was discontinued, and within the following days, the pruritic rash subsided. At that point, the patient was discharged home on immunosuppressive treatment with MMF only. Two weeks postdischarge, the transplantation team decided [5] to reintroduce TAC according to current guidelines for LT medications [6]. Unfortunately, this was followed by a recurrence of the pruritic rash. The relapse of symptoms was considered a positive drug provocation test, and the diagnosis of allergy to TAC was established. The patient was then placed on a mechanistic Target of Rapamycin (mTOR) inhibitor (everolimus [Certaican]) at a dose of 2 mg/d and remained asymptomatic.

Case 2

A 50-year-old male patient was grafted for secondary liver cirrhosis with a cadaveric liver. The patient was on immunosuppression with a TAC dose of 1 mg/d. In postoperative month 13, the patient developed varicella zoster virus infection and was admitted to the Organ Transplantation Unit for antiviral treatment. During hospitalization, the patient complained about pruritus affecting the whole body that had started several weeks before admission and was severely impairing his quality of life. The patient's laboratory investigations showed bile acids of 8.7 μ mol/L (standard value: 0.9-9 μ mol/L) and total and direct bilirubin of 1.97 and 1.07 mg/dL, respectively, which were within normal limits excluding bile stasis or graft disease. The patient reported chronic itch with no relief after treatment with UDCA, cholestyramine, and levocetirizine, which prompted further investigation for allergy to TAC. The allergy testing to TAC showed the following: SPTs were negative (histamine control test: 8 mm wheal). The IDTs were positive for the 1:1000 test solution with a 5 mm wheal and the 1:10 test solution with a 5 mm wheal (Fig 1B). TAC was discontinued, and an mTOR inhibitor (everolimus) at 2 mg/d was initiated. Pruritus improved significantly in the days following the intervention.

Case 3

A 70-year-old male patient diagnosed with alcoholic liver cirrhosis was subjected to an orthotopic LT. Immunosuppression was with MP, MMF, and cyclosporine (Neoral: 125 mg $\times$ 2 per os). In postoperative month 11, cyclosporin was discontinued because of renal toxicity, and the patient was placed on MMF and MP. Two months later, immunosuppressive treatment (TAC) was added in prolonged-release capsules at 1 mg/d. At that point, the patient's renal function tests were normal. Unfortunately, 4 hours after administering the first dose of TAC the patient developed edema in the inguinal area and erythematous pruritic rash on the left part of the abdominal wall [7]. He also complained about general itchiness that prompted a referral for allergy testing. Because of the symptoms concerning tacrolimus obtainment by the patient, further allergy testing was organized. SPTs to tacrolimus were negative (histamine control test: 8 mm wheal). The IDT with a 1:1000 dilution of the drug was positive with a 5 mm wheal (Fig 1C). Because of allergy diagnosis to TAC, the patient was switched to an mTOR

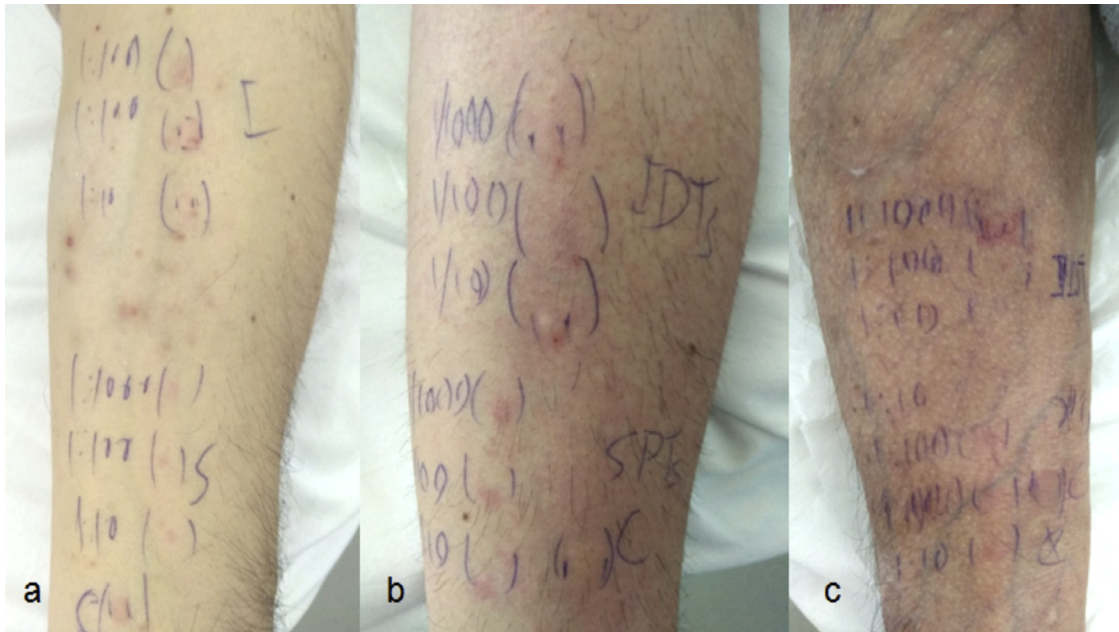


Fig 1. Diagnostic evaluation of the 3 patient cases by SPT and IDT. **(A)** The first patient (case 1) had a positive reaction at dilutions of 1:100 and 1:10 for IDT. The initial 1:1000 test was negative. The SPT yielded negative results. **(B)** The second patient (case 2) had positive reactions at dilutions of 1:1000 and 1:10 for IDT. The SPTs were negative. **(C)** The third patient (case 3) had a positive IDT at a dilution of 1:1000. The 1:100 and 1:10 test solutions were not performed because it was regarded as unnecessary to proceed to a higher concentration of IDT solution that could elicit a more severe reaction and more discomfort to the patient. The SPTs were negative. All 3 patients had a positive result when evaluated 1 hour after injection and remained positive for another 1 or 2 hours, suggesting a delayed hypersensitivity reaction. IDT, intradermal test; SPT, skin prick test.

inhibitor (everolimus) at a dose of 2 g/d. Subsequently, the patient's symptoms subsided, and he was completely relieved of any discomfort in a couple of days.

DISCUSSION

In the organ transplantation era, immunosuppression is fundamental for a successful outcome. TAC is a widely used agent in this field. Recently, a new TAC formula was recommended (ie, the prolonged release-capsules administered once daily). The allergic reaction to this agent is a controversial hypothesis because the main allergy symptoms of pruritus and skin redness [8] are common complications of LT in addition to elevated bilirubin and bile acid levels. Therefore, it is important in such patients to proceed with a meticulous investigation to exclude the disease entities [9] that result in elevated bilirubin and bile acid levels in LT patients, such as cholangitis episodes, various obstructive syndromes of the bile tree, or adverse events attributed drugs (ie, antibiotics, etc). The exclusion of the causes mentioned earlier and the persistence of symptoms, such as itching in the relief treatment, may put allergy to the immunosuppressive regimen in the picture. Allergy symptoms may overlap with symptoms caused by complications of the graft disease; thus, the diagnosis of a drug allergy may be missed. A sign of this is pruritus that remains after the treatment of liver complications.

In the current literature, there are a few reported cases regarding allergic reactions to TAC. In 2018, Trofe-Clark et al [10] investigated the possibility of cross-reactivity between macrolide antibiotics and the oral form of TAC in kidney transplant candidates and recipients. Eight patients who received kidney transplants had a positive history of macrolide allergy based on clinical criteria. They were all placed on oral TAC immunosuppression. They did not experience any allergic reaction to the drug, suggesting that a positive history of macrolide antibiotic allergy should not necessarily preclude posttransplant TAC use [10]. In 2020, Taghvaye-Masoumi et al [11] reported a case of a 19-year-old male patient who underwent a hematopoietic stem cell transplantation for thalassemia and had a history of TAC anaphylaxis. The reaction was attributed to the Cremophor EL polyoxyethylated castor oil, which acts as a carrier, solubilizer, and emulsifier in intravenous calcineurin inhibitors [11].

In this study, 3 male adult patients are presented who all experienced allergic reactions refractory to the symptomatic treatment with oral levocetirizine at therapeutic doses attributed to TAC in the form of prolonged-release capsules administered once daily as immunosuppression after an orthotopic LT. In all 3 cases, the allergic symptoms involved the skin, with the major clinical sign being severe pruritic rash. No severe types of delayed hypersensitivity reactions were present, such as Stevens-Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, or drug rash with

eosinophilia and systemic symptoms. Mild to moderate skin allergy symptoms usually have a benign clinical course, and in such cases, no skin biopsy is performed [7]. Skin lesions that are pathognomonic in severe drug hypersensitivity of delayed-type would be absent because T cell-driven reactions are highly suppressed in immunocompromised patients. The onset was related to the oral administration of the TAC and affected the whole body area. All the patients were unresponsive to treatment with UDCA, cholestyramine, and antihistamines. All the patients experienced alleviation of the severe itch immediately after stopping tacrolimus, and the extended rash disappeared in a few days. The 3 presented patient cases suffered from delayed-type hypersensitivity reactions [8,12] to the form of TAC mentioned previously. None of the 3 patients reported a cross-reactivity to macrolide antibiotics described by Riley et al or Kang et al [2,3]. On the contrary, the patients had received macrolides in the past without any adverse reactions. Sensitization to the immunosuppressive agent was owing to the long-term exposure to the drug through the daily oral route over several months. Management was with treatment cessation. None of our patients required emergency medication for relief from the allergy symptoms.

Regarding the allergy evaluation by SPTs and IDTs, no previous publications were available to decide the test solutions' optimum nonirritating concentrations and the appropriate dilutions for allergy testing. Regarding the sensitivity of the SPTs and the IDTs performed with the test solutions in the previously mentioned concentrations, the SPTs had a very low sensitivity. The tests did not recognize any of the allergic patients, whereas the IDTs were highly sensitive. The IDTs generally have a good sensitivity of 75% and a high specificity of 90% regarding drug allergy diagnosis [13] and a good correlation with atopy [14]. The delayed reading, which was 1 to 3 hours after the test solution had been injected, yielded a positive result in all 3 cases, suggestive of a delayed drug hypersensitivity reaction as described by Brockow et al [15-17]. A posttransplant food allergy was not considered a possible diagnosis because the patients had no clinical signs of food allergy while on an unrestricted diet [18].

Additional evidence supporting the issue of posttransplant-delayed hypersensitivity reactions to the aforementioned form of TAC is the relapse of pruritic rash after the reintroduction of TAC in the treatment of one of the presented patients. The relapse episode was regarded as a positive drug provocation test, which established the drug allergy diagnosis.

The implication of the adverse events to the drug excipients was ruled out by performing IDTs and patch tests in all the affected patients who were negative. Patch testing with the immunosuppressive agent itself (ie, TAC) is not currently recommended as these drugs inhibit the Langerhans cells. They also suppress the activation of T lymphocytes, key cells in allergic contact dermatitis [19].

Further observations would be needed to precisely identify patients who develop drug hypersensitivity reactions to immunosuppressive drugs and warrant appropriate allergy evaluation through allergy testing.

In the form of prolonged-release capsules, TAC administered once daily for immunosuppression in allogeneic organ-transplanted patients may cause allergic reactions of the delayed hypersensitivity type. The target organ is most commonly the skin, with the cardinal presentation being severe itch and generalized skin rash. Other causes of refractory to treatment skin itch, such as bile stasis or graft disease, need to be excluded. The IDTs performed in a concentration of 0.1 mg/mL (1:10) and its dilutions 1:100 and 1:1000 proved to be nonirritating and highly sensitive. They confirmed the clinical diagnosis of allergy to TAC in all 3 cases. Management was by discontinuing the drug. Cessation of the culprit agent was followed by symptom resolution, and the immunosuppressive treatment was continued with alternative medications.

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