一、閱讀以下文章摘要並回答問題（共 16 分）

Impact of direct-acting antivirals for hepatitis C virus therapy on tacrolimus dosing in liver transplant recipients by Bixby AL, *et al.*

Introduction

Direct-acting antivirals (DAAs) have transformed hepatitis C virus (HCV) management post-liver transplant. As HCV clears during DAA treatment, hepatic metabolism improves, resulting in decreased tacrolimus concentrations that may require dose adjustment. The purpose of this study was to determine appropriate management of immunosuppression in liver transplant recipients during and following treatment of HCV.

Methods

This study was a single-center retrospective analysis of 71 liver transplant recipients who were treated for HCV with DAAs. The primary outcome was change in dose-normalized tacrolimus concentrations from the start of DAA treatment to 12 weeks following therapy.

Results

The mean change in log-transformed dose-normalized tacrolimus concentrations was a reduction of 0.43 ng/mL/mg (95% CI; 0.26-0.60, $P < 0.0001$). The greatest decrease occurred in the first 4 weeks of treatment, after which levels stabilized. The overall mean tacrolimus concentration was 4.8 ng/mL (±2.5). **Two patients (3%) developed acute cellular rejection and two patients (3%) had graft loss and died.**

Conclusion: From the start of treatment to 12 weeks post-DAA therapy, liver transplant recipients experienced a significant decrease in dose-normalized tacrolimus concentrations. In conclusion, close monitoring of tacrolimus concentrations is warranted during and following treatment with DAAs, as dose increases may be indicated in order to maintain therapeutic concentrations to prevent graft rejection.

Transpl Infect Dis. 2019 Jun;21(3):e13078.

1. 將有底線粗體的 3 句英文逐字翻譯成中文。（6 分）
2. 試舉一例可涵蓋 C 型肝炎病毒全基因型的 direct-acting antiviral (DAA) 學名、作用機轉、以及涵蓋哪些基因型。（6 分）
3. DAA 中含 ombitasvir、paritaprevir、ritonavir 之複方錠劑 Viekirax 維建樂®會增加 tacrolimus 的血中濃度，一般而言不建議兩者併用。最可能的交互作用機轉是什麼？試說明之。（4 分）

見背面

二、就下列處方回答問題：(共 9 分)

A. 此張處方缺乏什麼資訊？還需要哪些資訊才能評估此處方的適當性？（3 分）

B. 這張處方有何問題？合理的處方應該為何？（3 分）

C. 請問藥師應如何發揮專業處理這張處方的問題？處理完後，應完成哪些藥師專業應做的工作？（3 分）

臺大醫院　　國立臺灣大學醫學院附設醫院

院址：臺北市中山南路 7 號　臺北市常德街一號

⊕NTUH　　網址：http://ntuh.mc.ntu.edu.tw

2019/08/10 14:35　　臺大醫院門診調劑單

病人姓名 陳 XX	女士	領藥窗口	09
年齡 028 性別 女	58 Kg 身份 N01	領藥號碼	L-8173
科別 FAM	醫師 李 XX	病人姓名	陳 XX
診斷 346.0	Migraine	處方日期	2019/08/10
401.0	Hypertension	病歷號碼	225xxxx
487.1	Influenza	結帳號碼	530xxxx
調劑藥師 王 XX	複核藥師 朱 XX	第 次領藥	

-- 共 04 種

Y	01	TAMIFLU 75 MG (OSELTAMIVIR CAPSULES)	PO	1	CAP	QD	5 TAB 5 天
Y	02	IBUPROFEN 400 MG (IBUPROFEN TABLETS)	PO	1	TAB	Q6H	40 TAB 10 天
Y	03	COZAAR 50 MG (LOSARTAN POTASSIUM TABLETS)	PO	1	TAB	QQ	28 TAB 28 天
Y	04	SYNBOT 5 MG (ENALAPRIL MALEATE TABLETS)	PO	1	TAB	BID	56 TAB 28 天

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三、閱讀以下文章摘要並回答問題（共 15 分）

Metoprolol for the prevention of acute exacerbations of COPD by Dransfield MT, *et al.*

Background

Observational studies suggest that beta-blockers may reduce the risk of exacerbations and death in patients with moderate or severe chronic obstructive pulmonary disease (COPD), but these findings have not been confirmed in randomized trials.

Methods

In this prospective, randomized trial, we assigned patients between the ages of 40 and 85 years who had COPD to receive either a beta-blocker (extended-release metoprolol) or placebo. **<u>All the patients had a clinical history of COPD, along with moderate airflow limitation and an increased risk of exacerbations, as evidenced by a history of exacerbations during the previous year or the prescribed use of supplemental oxygen.</u>** We excluded patients who were already taking a beta-blocker or who had an established indication for the use of such drugs. The primary end point was the time until the first exacerbation of COPD during the treatment period, which ranged from 336 to 350 days, depending on the adjusted dose of metoprolol.

Results

A total of 532 patients underwent randomization. The mean (±SD) age of the patients was 65.0±7.8 years; the mean forced expiratory volume in 1 second (FEV1) was 41.1±16.3% of the predicted value. The trial was stopped early because of futility with respect to the primary end point and safety concerns. There was no significant between group difference in the median time until the first exacerbation, which was 202 days in the metoprolol group and 222 days in the placebo group (hazard ratio for metoprolol vs. placebo, 1.05; 95% confidence interval [CI], 0.84 to 1.32; P = 0.66). Metoprolol was associated with a higher risk of exacerbation leading to hospitalization (hazard ratio, 1.91; 95% CI, 1.29 to 2.83). The frequency of side effects that were possibly related to metoprolol was similar in the two groups, as was the overall rate of nonrespiratory serious adverse events. During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group.

Conclusion:

<u>Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group.</u> Hospitalization for exacerbation was more common among the patients treated with metoprolol.

N Engl J Med 2019;381:2304-14.

1. 將有底線粗體的 2 句英文逐字翻譯成中文。（4 分）
2. 以中文說明為何此研究提前終止。優缺點分別是什麼？（3 分）
3. 試從藥物作用機轉推測此研究結果是否可外推至其他 beta-blocker，包括 atenolol、carvedilol、propranolol。分別是什麼原因？（8 分）

見背面

四、請依下述臨床案例描述回答對(O)或錯(X)。(7 題，共 30 分)

Mrs. Wang aged 60 experienced orthostasis and diarrhea after attending a meeting. She's been in good health without any complaints nor any medications other than oral ibuprofen 400 mg Q 6 h p.r.n. for headache and arthritis in the past months. Laboratory data showed Hb 7.5 g/dL, Hct 25% and guaiac-positive stool. Endoscopy revealed an antral ulcer 0.5 cm. No duodenal ulcers were found.

Answer True (O) or False (X) to the following statements.

1. The laboratory data rule out Mrs. Wang has GI bleeding. (4 分)
2. Ibuprofen is the cause of antral ulcer and GI bleeding. (4 分)
3. NSAID-associated ulcers do not correlate well with pain and the analgesic action of ibuprofen possibly mask the epigastric pain. (4 分)
4. The orthostasis is merely reflective of volume loss secondary to GI bleeding. (4 分)
5. Rectal or IV administration of ibuprofen will attenuate GI damage due to the absence of direct mucosa contact. (4 分)
6. Celecoxib, a COX-2 specific inhibitor, is known to respond for anti-inflammatory and analgesic effects. Therefore, Mrs. Wang could replace ibuprofen with celecoxib to treat arthritis problem. (4 分)
7. If Mrs. Wang has a H. pylori test negative, H2-blockers are the drug of choice for ulcer healing. 8. The proton pump inhibitor is preferred over a H2-blocker when Mrs. Wang must continue with NSAID for management of arthritis. (6 分)

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五、單選題 (30 分，2 分/題)：※ 注意：請於試卷內之「選擇題作答區」依序作答。

1. Guidance statements from American Society of Clinical Oncology (ASCO) and International Society on Thrombosis and Haemostasis (ISTH) recommend the use of novel oral anticoagulants (NOACs) as primary thromboprophylaxis in ambulatory patients with cancer who are starting chemotherapy. Which NOACs are recommended for thromboprophylaxis in patients with cancer?
(A) Dabigatran and edoxaban
(B) Rivaroxaban and apixaban
(C) Rivaroxaban and edoxaban
(D) Apixaban and dabigatran

2. A patient with which of the following cancers would be at highest risk of thrombosis, as determined by the Khorana score?
(A) Stomach
(B) Gynecologic
(C) Lung
(D) Lymphoma

3. Which of the following factors would best help distinguish bipolar depression from unipolar depression?
(A) Decreased appetite
(B) Lack of interest in things that are typically enjoyed
(C) Difficulty concentrating
(D) Frequent recurrence of depressive symptoms

4. A 13-year-old girl, considered overweight with a BMI at 87th percentile for age, is diagnosed with bipolar depression. Which of the following treatments would you select as most appropriate acute treatment to reduce depressive symptoms with minimal impact on weight or metabolic parameters?
(A) Lamotrigine
(B) Quetiapine
(C) Lurasidone
(D) Olanzapine/fluoxetine combination

5. Which of the following statements best describes why therapies beyond PD-1, PD-L1, and CTLA-4 are needed?
(A) Immune checkpoint inhibitors targeting PD-1, PD-L1 and CTLA-4 are effective in 80% to 90% of patients in the most responsive of tumor types.
(B) Immune stimulatory agents have been shown to be more effective
(C) Response rates may be improved with novel monotherapies or combination therapies.
(D) Innate resistance to PD-1-, PD-L1-, and CTLA-4-based therapies is occurring more frequently.

6. Which of the following is true regarding the mechanism of action of hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitors (PHIs)?
(A) They decrease iron mobilization to the bone marrow.
(B) They block enzymes and facilitate endogenous physiologic mechanism of erythropoiesis.
(C) They bind to erythropoietin receptors and stimulate erythropoiesis.
(D) They enhance the degradation of HIF-α, resulting in enhanced erythropoietic gene transcription.

7. Which of the following best describes the use of iron therapy in clinical trials assessing the use of HIF-PHIs in treating anemia in patients with nondialysis-dependent chronic kidney disease?

見背面

(A) Anemia was treated in patients in the HIF-PHI arm, only with concomitant intravenous iron therapy.
(B) Anemia was treated in patients treated with HIF-PHI irrespective of iron status.
(C) Anemia was treated in patients in the HIF-PHI arm but also showed higher rates of reactive IV iron injections.
(D) Anemia was treated in patients in the HIF-PHI arm only after correction of iron status.

8. Henry is a 54-year-old piano teacher with a 5-year history of RA. He presents to the clinic for his 6-month follow-up visit. During the examination, he mentions that he is experiencing pain and tenderness in his joints and has had to cancel piano lessons recently, due to his increasing fatigue. His 28 Joint Disease Activity Score (DAS28) has increased from 2.9 at his past visit to 3.6 today. He is currently on infliximab and has received 4 infusions. His previous treatment regimens included methotrexate (MTX) monotherapy and adalimumab in combination with MTX. He is discouraged with the progress of his current treatment plan, and he also mentions the burden of driving for several hours to receive his infusion. He is worried about losing more students due to his availability. In addition, he expresses some reservation about self-injection, noting that it would take him over an hour to "psych himself up" for the adalimumab injections. What would be the next best step for Henry?
(A) Continue infliximab and ask Henry to follow up in 3 months.
(B) Discontinue the current treatment regimen and start abatacept.
(C) Discontinue the current treatment regimen and start a JAK inhibitor.
(D) Discontinue the current treatment regimen and start tocilizumab.

9. Which of the following analgesic therapies is not recommended as an option to reduce the risk of transitioning from acute to chronic pain for musculoskeletal pain?
(A) Nonsteroidal anti-inflammatory drugs (NSAIDs)
(B) Opioids
(C) Gabapentanoids
(D) Serotonin-norepinephrine reuptake inhibitors (SNRIs)

10. Before an elective intervention associated with a high risk of bleeding, what is the recommended duration of interruption of factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) before the day of surgery?
(A) No interruption
(B) 24 hours
(C) 48 hours
(D) 72 hours

11. Nina is a 52-year-old woman with a history of asthma that began in childhood and has been well-managed the majority of her life. Nina recently moved to a colder climate and started a new job. Today she is presenting with erythematous papules around the eyes and back of her neck, as well as conjunctivitis. Based on Nina's presentation and medical history, what would you suspect first?
(A) Contact dermatitis
(B) Atopic dermatitis
(C) Stress rash
(D) Scabies

12. Catherine is a 65-year-old woman with a 10-year history of type 2 diabetes. She presents to her primary care clinician complaining of being increasingly tired and continues to forget to take her prescribed medications. After physical examination, her BP is 150/95 mmHg, BMI is 34 kg/m2; lab data showing that her LDL is 150 mg/dL, glycated hemoglobin is 8.3%, and estimated glomerular filtration rate (eGFR) is 70 mL/min/1.73 m2. There is no family history of diabetes. Which clinical risk factor will be the leading cause of Catherine's chronic kidney disease?
(A) Type 2 DM

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(B) Dyslipidemia
(C) Hypertension
(D) Obesity

13. When assessing for kidney disease, GFR is only one important component to consider. Urinary albumin-to-creatinine ratio (ACR) is now recognized to be key in risk assessment, as it is a marker for kidney disease, inflammation, and cardiovascular risk. Which one is a sign indicating progression towards nephropathy?
(A) < 30 mg/g
(B) 30-300 mg/g
(C) > 300 mg/g
(D) > 500 mg/g

14. Which of the following best describes the pathophysiology associated with guanylate cyclase in patients with heart failure, under conditions of oxidative stress?
(A) Reduced levels of circulating nitric oxide (NO), preventing the stimulation of GC and attenuation of downstream cardioprotective mediators
(B) Enhanced levels of NO inhibit GC, which prevents the activation of downstream cardioprotective mediators
(C) Downregulation of GC causes inability to bind circulating NO to activate downstream cardioprotective mediators
(D) Increased NO levels lead to GC activation, which inhibits downstream cardioprotective mediators

15. Which of the following describes a rationale for targeting novel therapeutic approaches, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and vericiguat, for treating patients with HF?
(A) Avoid resistance to currently available agents
(B) Reduce the residual risk associated with currently available agents
(C) Overcome receptor desensitization that occurs with currently available agents
(D) Improve safety profile and adherence