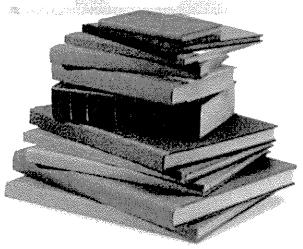
感染知識



今回のテーマ

肺結核

国立病院機構東京病院外来診療部長
永井 英明

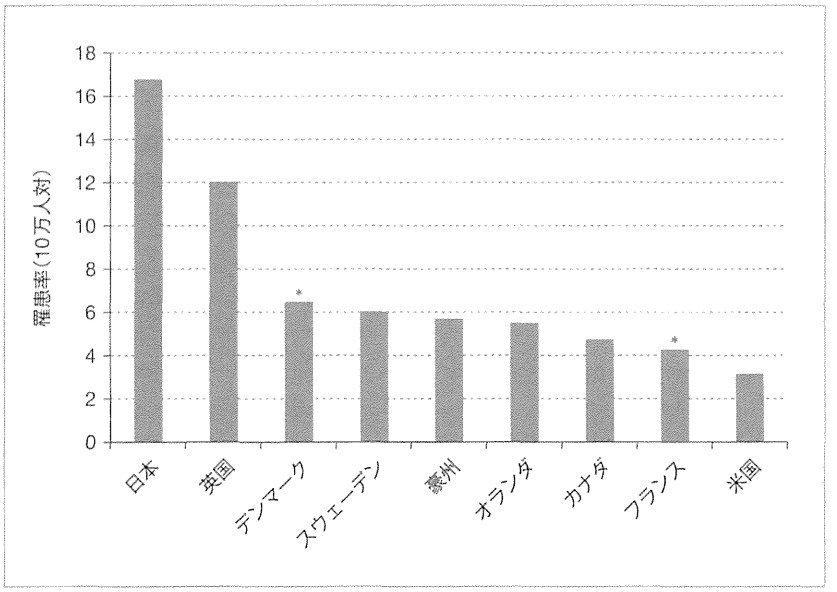


図1　諸外国と日本の結核罹患率
＊は2011年データ，他は2012年データ。

(文献1より引用)

年以降に横ばいとなったが，2008年以降は再び増加に転じている。80～84歳の結核患者数は横ばいであり減っていない。

外国出生者の新登録結核患者数は年々増加しており，特に若年層の新登録患者の外国出生者割合が大きく，20歳代では新登録結核患者の3分の1以上は外国出生者である[1]。

受診の遅れと診断の遅れが相変わらず認められており，結核感染対策という視点に立てば改善されなければならない。有症状結核のうち，症状発現から初診までの期間が2ヵ月以上(受診の遅れ)の割合は18.7%(2012年)であり，働き盛りの30～59歳に限ってみると33.7%と3人に1人は受診が遅れている[1]。受診の遅れの間に多数の人々に感染を広げている可能性がある。有症状結核のうち，初診から診断までの期間が1ヵ月以上(診断の遅れ)の割合は22.0%であり[1]，医療機関における結核診断の遅れが依然として認められ，医療従事者の結核診断の甘さがみられる。院内感染対策上，問題である。結核の中蔓延国である日本では，長引く咳や胸部異常影のある症例では喀痰の抗酸菌培養検査を，日にちを変えて3回必ず行うべきである。

結核の感染様式

結核患者の咳やくしゃみにより，結核菌を含んだ飛沫が空気中に飛散し，これらの飛沫は乾燥して水蒸気を失うと，内部にあった菌体が空中に浮遊することになる。これを飛沫核といい，飛沫核が吸入されることによって結核

感染が成立する。いわゆる飛沫核感染(空気感染)である。排菌者とどの程度の期間接すると感染が成立するかは，排菌量，咳の強さ，接する側の免疫機能などで修飾されるため正確なデータはないが，従来の院内感染の事例をみると，排菌者との接触が数時間から数日以内という短期間にもかかわらず感染が成立している例もある。したがって，短期間でも感染が成立する可能性が常にあることを認識していなければならない。

患者が塗抹陽性痰を喀出している間は，培養のみ陽性の場合と異なり菌量が多いので，結核の感染力は強い。喀痰塗抹陽性患者の痰の中には1mLあたり7,000個以上の結核菌が存在している。感染危険率(感染させるリスク)を塗抹・培養ともに陰性の患者に比べると塗抹陽性患者は10倍，塗抹陰性・培養陽性患者は2倍といわれている。塗抹陽性患者に対しては，結核感染を広めないための公衆衛生的対応が必要である。

肺結核の診断

胸部X線写真では，上葉を中心とする空洞影とその周辺に多発小粒状影を伴う陰影が典型的であるが，胸水貯留，縦隔リンパ節腫大を認めることもある。肺結核の進展は基本的には気道散布であり，それを端的に示す胸部X線所見は多発小粒状影である。それは終末細気管支から肺胞道周辺に形成される結核性病変を反映しており，散布性粒状影ともいわれる。CTでは小葉中心性の粒状影として認められ，ときに分岐状影を呈する。粒状影とそれを連結する細気管支の樹枝状陰影を，tree-in-bud(図2)といい，結核病変としては特徴的であり，他の疾患を否定する重要な所見となる。

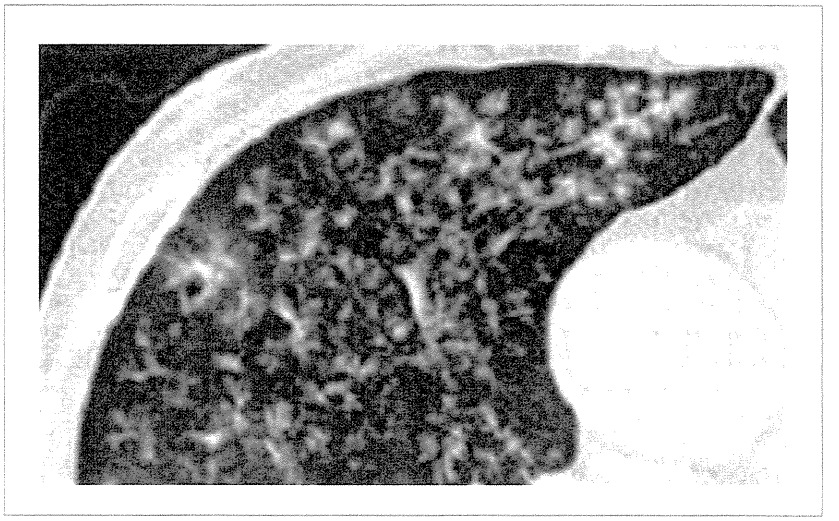


図2　Tree-in-bud像
終末細気管支から肺胞道周辺に形成される結核性病変。

肺結核の診断は喀痰の塗抹・培養検査において結核菌を検出することにより確定する。喀痰検査で結核菌を検出できない場合は，胃液検査あるいは気管支鏡検査を行い病変部の気管支洗浄，肺生検を行う。喀痰塗抹検査は，現在では集菌法が用いられており，ガフキー号数ではなく(1+)，(2+)，(3+)という記載法が行われている。菌の同定には，喀痰などの臨床検体を用いて，結核菌のRNAやDNAを増幅する方法が汎用されている。培養菌についても同様に核酸同定法が一般的になっている。

結核の治療

結核患者の体内に生存する結核菌を撲滅するためには，患者の結核菌に有効な，作用機序の異なる抗結核薬を3剤以上組み合わせた多剤併用療法を，決められた期間継続して投与する必要がある。多剤耐性結核患者の発生を抑止するためには治療を確実に完遂することが重要である。

感受性菌の場合，4剤併用療法が「菌の撲滅」という治療目標を達成し得る最強の治療法であり，かつ6ヵ月(180日)間で治療を完了し得る最短の治療法として，すでに世界中に広く普及している。

1. 初回治療患者の標準療法[3](図3)

(A)法：リファンピシン(RFP)＋イソニアジド(INH)＋ピラジナミド(PZA)にストレプトマイシン(SM)〔またはエタンブトール(EB)〕の4剤併用で2ヵ月間治療後，RFP＋INHで4ヵ月間治療する。

(B)法：RFP＋INH+SM(or EB)で2ヵ月間治療後，RFP＋INHで7ヵ月間治療する。

EBまたはSMを3ヵ月目以降の維持期に使用する意義は少なく，またこれらの薬剤は長期に使用することにより副作用の危険性も高まるので，原則として3ヵ月目以降は中止する。

通常は標準治療法(A)法を選択する。高齢者などPZAを投与できない

標準治療法(A)	PZA					
	EB (SM)					
	INH					
	RFP					
病月	1	2	3	4	5	6

標準治療法(B)	EB (SM)								
	INH								
	RFP								
病月	1	2	3	4	5	6	7	8	9

図3　結核初回治療患者の標準療法

原則(A)法を用いて，PZAが投与できないときに(B)法。
標準治療法の維持期はINH，RFPの2剤。
耐性菌と判明した時点で治療薬を変更。
PZA：ピラジナミド，EB：エタンブトール，SM：ストレプトマイシン，INH：イソニアジド，RFP：リファンピシン。

例に対しては，標準治療法(B)法を選択する。EB耐性よりもSM耐性の頻度が高いので，初期2ヵ月は通常はEBを選択する。INH，RFPともに感受性であることが確認された時点で，EB(またはSM)は終了する。

(A)法は6ヵ月(180日)間，(B)法は9ヵ月(270日)間を標準的治療期間とする。

ただし，粟粒結核や病型分類1型などの重症例，2ヵ月を超える培養陽性例，再治療例，糖尿病や塵肺合併例，全身的なステロイド薬・免疫抑制薬併用例，HIV感染症などでは3ヵ月(90日)間延長することができる。これらの要素が複数あっても原則として3ヵ月間の延長でよい。なお，4ヵ月を超える排菌持続例では菌の耐性化を考慮して，直近の菌を用いた感受性検査を再検することが望ましい。

2. 間欠療法

2008年の「結核医療の基準」の見直しで，間欠療法が提案された[3]。

間欠療法は少ない服薬回数で，確実な治療継続の確保が可能な治療法であり，諸外国ではすでに行われている。間欠療法が行えるのは，PZAを加えた標準治療(A)法の2ヵ月間の初期治療が確実に行われ，RFP，INHの両剤に感受性であることが確認された症例である。HIV感染者では間欠療法を行ってはいけない。

間欠療法は初期2ヵ月間4剤の治療終了後，RFPとINHの2剤を4ヵ月間週2回，または週3回服用する。広汎空洞型では週3回とする。薬剤投与量は，RFPは標準治療と同じ量である。INHは初期2ヵ月間は標準治療と同じ量であるが，間欠期は15mg/kg，1日最大投与量900mgである。服薬がおろそかになると治療失敗につながるので，必ず対面服薬確認法を行う。

抗結核薬の副作用

感受性菌であれば，結核の治療は比較的容易である。しかし薬剤の副作用のために，ときに治療を中断しなければならないこともあり，すべての薬剤の副作用について熟知していなければならない。代表的な副作用としては，肝障害〔RFP，PZA，エチオナミド(TH)，INH〕，視神経炎(EB)，聴力・平衡障害(アミノグリコシド系薬剤)，皮膚症状〔RFP，PZA，INH，EB，パラアミノサリチル酸(PAS)など〕，腎障害(アミノグリコシド系薬剤，RFP)などがある。

RFPまたはINHのアレルギー様副作用(発疹・発熱など)が疑われる場合にはその投与を中止せざるを得ないことがある。しかし，副作用の回復後，ただちに減感作療法を試みるべきである。最も強力な抗結核薬であるRFPやINHを外した治療は，治療の長期化を招き不十分な治療となる可能性があるからである。

最近の話題
(詳しくは本誌別項参照)

結核感染の診断はツベルクリン反応に替わって，インターフェロン-γ(IFN-γ)遊離測定法(interferon-gamma release assay：IGRA)が行われている。IGRAは特異的抗原刺激に対するリンパ球のIFN-γ産生能を測定することによって結核感染の診断を行う方法である。現在，わが国で用いられているIGRAはQuantiFERON®-TB GoldとT-SPOT®.TBである。IGRAはBCG接種の影響を受けず，感度，特異度ともに優れた結核感染診断法であり，BCG接種を行ってきたわが国では，接触者健診および医療従事者の健診にIGRAは有用である。しかし，経験を積むにつれ，検体の扱い・処理の仕方が結果に及ぼす影響，免疫不全状態での感度・特異度の低下，リンパ球数の結果に及ぼす影響，不安定な再現性・変動の問題などが指摘されてきた。

2つのIGRAでは「判定保留」の意味も異なるなど，違いを認識する必要がある。両者とも生きた細胞を扱うので，検体の扱いを含めた精度管理が重要である。

不適切な治療や患者管理は耐性菌の排出を増加させる可能性がある。耐性結核菌は10種類ある抗結核薬のいずれかに耐性の結核菌を指すが，最も強力な治療薬であるINHとRFPの両剤に耐性である耐性菌による結核を多剤耐性結核(multidrug-resistant tuberculosis：MDR-TB）という。MDR-TBの治療薬としてデラマニドが承認された。しかし，デラマニドの使用については日本結核病学会治療委員会が使用指針を出すことになっている。安易な使用により耐性化をもたらしてはならないので，使用には制限が設けられる。

IGRAについては本誌の別項を参照されたい。

[文献]

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Memorial Lecture by Imamura Award Winner

STUDY OF TUBERCULOSIS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Hideaki NAGAI

Abstract The research on tuberculosis (TB) comorbid with human immunodeficiency virus infections (HIV/TB), for which this prize was awarded, began with the author's experience with Japan's first HIV/TB case in 1992. In 1997, the clinical characteristics of six HIV/TB cases were presented in the *Japanese Journal of Thoracic Diseases*. In 2001, the author published a paper in *Kekkaku* on the anti-HIV antibody positive rate of TB patients. As part of a research team with the Japanese Ministry of Health, Labour and Welfare (2011-2013), the author surveyed the HIV/TB patients in the National Hospital Organization, and found a more or less unchanging mean 0.39% HIV-positive rate among TB patients. Among these TB cases, 2.1% were multidrug-resistant TB. In 2007, the results of QuantiFERON®-TB-2G (QFT-2G) HIV/TB analysis were reported in *Kekkaku*, showing the usefulness of QFT-2G in immunosuppression cases. Positive rates obtained with QFT-2G and QuantiFERON®-TB Gold (QFT-3G) declined when the peripheral blood lymphocyte count decreased, thought to be a result of QFT's whole-blood collection methods. The author further studied the usefulness of interferon-gamma release assays (IGRAs) in HIV/TB with another health ministry research team (2009-2011). Enzyme-linked immunospot assay and QFT-3G were compared, which yielded better sensitivity and fewer indeterminate cases with the former. Periodic IGRAs were performed in IGRA-positive patients. Ten such cases (2 received isoniazid) were observed for more than 3 years, but none developed TB; however, IGRA values fluctuated during the observation period. It seems highly likely that immune function recovery through antiretroviral therapy lowered the risk of developing active TB. The author further examined the therapeutic interaction of rifampicin with anti-HIV drugs, confirming the feasibility of combining efavirenz and raltegravir. These results were presented at the annual meeting of the Japanese Society for Tuberculosis in Tokyo in 2012. The author intends to continue research with the hope of reducing HIV/TB incidence and improving prognosis.

Key words: Human immunodeficiency virus, Acquired immune deficiency syndrome, Tuberculosis, Interferon-gamma release assay, Multidrug-resistant tuberculosis, Efavirenz, Raltegravir

Introduction

The risk of developing active tuberculosis (TB) increases in many immunodeficient states but is highest in cases of human immunodeficiency (HIV) infection, which involve a marked decline in cellular immunity.

Japan's TB prevalence has declined to 16.1 cases per 100,000 people (2013); however, among other Western nations, prevalence is no more than five cases per 100,000 people, meaning TB is still moderately prevalent in Japan. The number of HIV/AIDS patients in Japan increased until 2008, eventually exceeding 1,500 new cases per year. Growth plateaued in 2009 but rose again in 2013 to the second-highest number of reported cases ever. In this environment, the number of comorbid HIV/TB cases appears unlikely to decrease.

The author treated Japan's first case of HIV/TB at Tokyo National Hospital in 1992[1]. By 1997, the author's team reported a summary of six cases[2], and, to date, the author has experienced 85 HIV/TB cases. Since that initial case, the author has engaged in a variety of research on HIV/TB. The main findings are described below.

1. Surveying changes in HIV-positive rates among TB patients in Japan

The number of HIV/TB patients seen at Tokyo National Hospital has increased yearly since 1992. In most cases, an HIV test is performed if the TB is miliary or nonspecific, but some cases of classical pulmonary TB are found to be HIV-positive purely by chance. Thus, to examine the true extent of HIV-positivity among TB patients, we performed HIV tests on

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all consenting TB patients for 2 years starting in January 1998[3]. In all, HIV tests were performed on 164 TB patients (4 HIV-positive) in 1998 and on 149 patients (6 HIV-positive) in 1999, amounting to a 3.2% HIV-positive rate for the 2 years. Typically not suspected of being HIV-positive, only 1.0% of classical pulmonary TB cases were positive for HIV, but miliary TB cases exhibited a high HIV-positive rate of 28.6%. As TB patients in the Tokyo area may have a high rate of HIV infection, it is important to test TB patients for HIV so infections can be discovered and treatment initiated earlier.

We also conducted fact-finding surveys of National Hospital Organization hospitals nationwide regarding HIV/TB and multidrug-resistant TB (MDR-TB) from 2007 to 2012[4]. Little variation was seen in HIV-positive rates among TB patients, ranging from 0.29% to 0.46% (mean 0.39%) (Table). There were 96 cases of HIV/TB in total, but 82 (85.4%) of these were concentrated in the major urban centers of Tokyo, Osaka, and Nagoya. These regions combined had a 0.91% HIV-positive rate, higher than other, more rural regions. Accordingly, we recommended promoting HIV screening of TB patients in major urban areas. The male-female ratio of the HIV/TB patients was 18:1, and patients' median age was 43 years. In 56% of cases, HIV positivity was discovered owing to TB onset. The mean CD4 count was 156/μL, with many cases of reduced immune function. There were 48 cases of pulmonary TB, and 39 cases of extrapulmonary TB (25 of which were miliary TB). Side effects due to antitubercular agents were common, occurring in 53 of 83 cases (63.9%). While being treated for TB, 42 patients began antiretroviral therapy (ART). Immune reconstitution inflammatory syndrome was observed in 16 of the 26 patients (62%) who began ART within 8 weeks of starting TB therapy. All seven patients who began ART within 4 weeks of starting TB therapy developed the syndrome. There were two cases (2.1%) of MDR-TB, of which one patient was a foreign national. No cases of MDR-TB have been found since 2009, so there appears to be no increasing trend.

2. The usefulness of interferon-gamma release assays (IGRAs) in HIV/TB

The risk of TB infection is extremely high in cases of HIV infection. In recent years, IGRAs have been more frequently used for diagnosing TB infection than the tuberculin skin test (TST). Forms of IGRAs include QuantiFERON®-TB-2G (QFT-2G), QuantiFERON®-TB Gold (QFT-3G), and T-SPOT®TB (T-SPOT); the latter two are currently in use. In 2006, the QFT-2G was the first to be put to use. It has superior sensitivity and specificity, but in cases of HIV infection with markedly reduced cellular immunity, we expected sensitivity to decrease and the number of indeterminate cases to increase. To examine this assumption, we studied the usefulness of QFT-2G in cases of HIV infection[5]. We examined the QFT-2G results, CD4 count, and the TST results in known cases of HIV/TB. In 13 HIV/TB cases, QFT-2G's sensitivity was 76.9%, significantly higher than that of the TST (erythema 38.5%, induration 15.4%). The one indeterminate case had the lowest CD4 count (16/μL). Thus, we considered QFT-2G highly sensitive and sufficiently useful in HIV/TB, although HIV cases with very low CD4 count may return indeterminate results.

Table Cases of TB patients with HIV infection in National Hospital Organization hospitals

Year	No. of TB patients	No. of HIV-positive TB patients	No. of HIV-positive MDR-TB patients
2007	4388	15 (0.34%)	1
2008	4165	19 (0.46)	1
2009	4129	18 (0.44)	0
2010	4122	16 (0.39)	0
2011	4091	18 (0.44)	0
2012	3502	10 (0.29)	0
Total	24397	96 (0.39)	2

Next, QFT-2G and enzyme-linked immunospot assay (ELISPOT; this study used T-SPOT) were performed simultaneously on 230 pulmonary TB patients with positive tubercle bacilli cultures[6]. Sensitivity was compared based on the lymphocyte count. The overall positive rates were 74% for QFT-2G and 92% for ELISPOT, showing better sensitivity in the latter. In the group with a lymphocyte count of 1,000/μL or more, QFT-2G's positive rate was 88% and ELISPOT's was 97%. With a lymphocyte count of 500/μL or less, the positive rate with QFT-2G was 39% and 81% with ELISPOT, a marked decline in QFT-2G's accurate, conclusive positive rate (Fig. 1). A comparison of QFT-3G and ELISPOT produced similar results. That is, when lymphocyte count declined, the positive rate of QFT-3G declined, and the number of indeterminate cases increased (Fig. 2).

We used periodic, simultaneous tests to compare the positive rates of QFT-3G and ELISPOT in HIV-infected patients[7], performing QFT-3G as many as 50 times in 35 HIV-infected patients. Cases that were indeterminate or equivocal using QFT were not found with ELISPOT. There were 13 positive cases diagnosed with QFT versus 22 positive cases with ELISPOT. Patients were grouped per 100/μL of CD4 to compare QFT-3G and ELISPOT (Fig. 3). In all count groups, the ELISPOT positive rate was the same or higher. In the CD4 200/μL or less group, three cases were indeterminate by using QFT-3G. No cases were indeterminate by using ELISPOT, which found two negative cases and one positive case.

The results of the previous studies ultimately show that when the CD4 count declines, the sensitivity of QFT-3G decreases, and the number of indeterminate cases increases. The ELISPOT test was not influenced by CD4 count, indicating the effectiveness of this test in cases of reduced immune function.

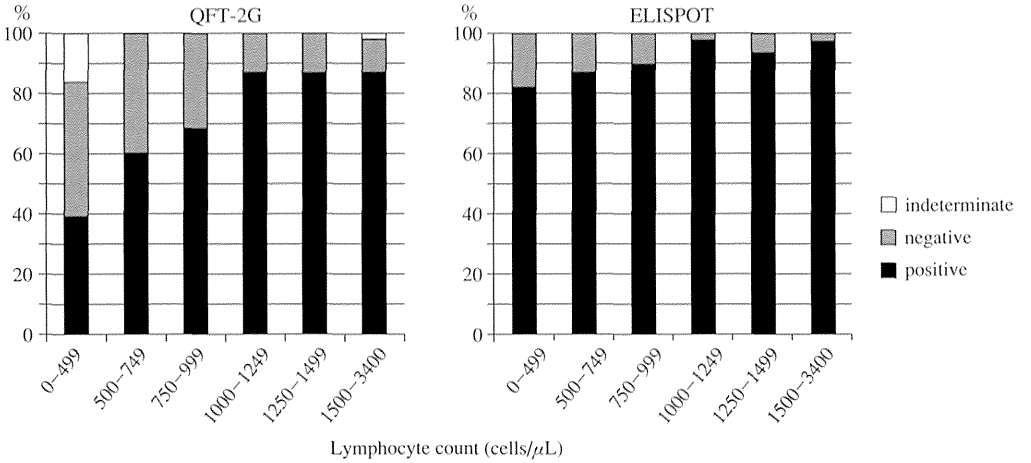

Fig. 1 Influence of lymphocyte count on QFT-2G and ELISPOT performance in pulmonary TB patients

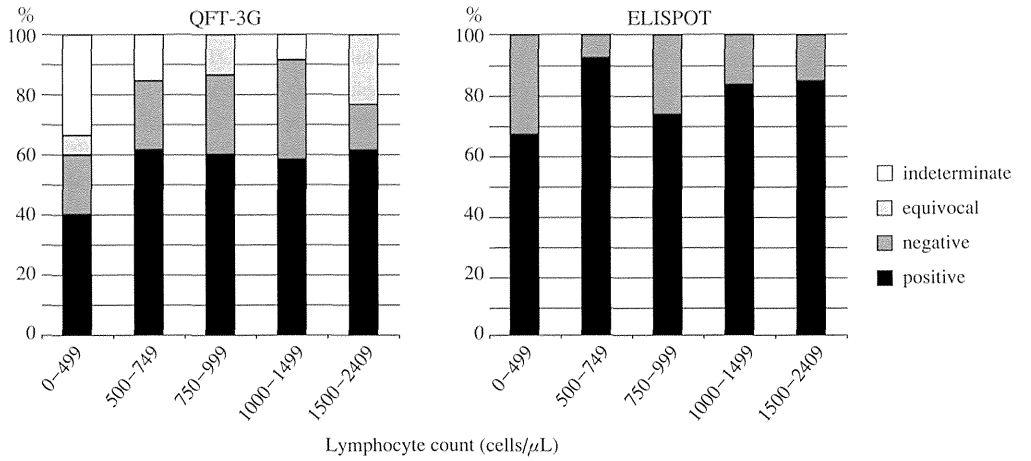

Fig. 2 Influence of lymphocyte count on QFT-3G and ELISPOT performance in pulmonary TB patients

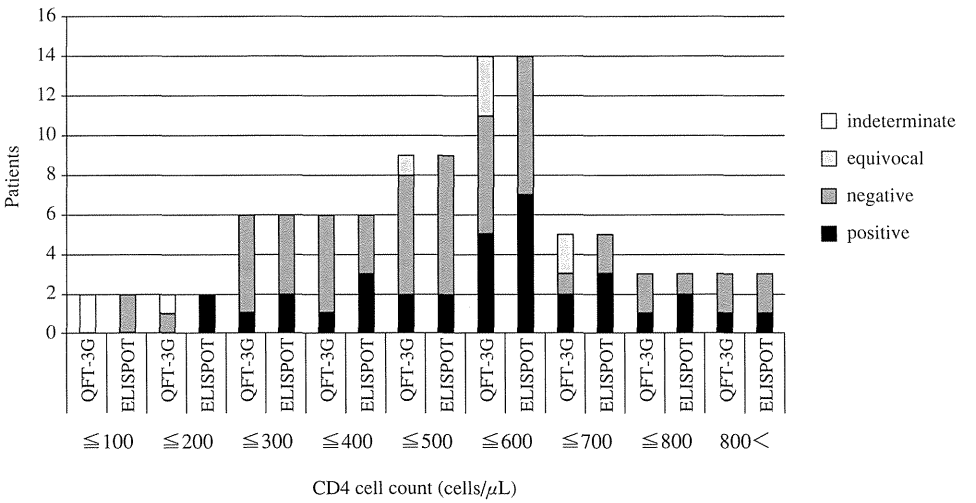

Fig. 3 Influence of lymphocyte count on QFT-3G and ELISPOT performance in HIV/TB patients

3. Research on the early discovery and treatment of latent tuberculosis infection comorbid with HIV infection

As IGRAs can become positive in HIV-infected patients undergoing ART, we sought to determine if TB would unavoidably occur in the future, or if isoniazid (INH) administration could suppress developing active TB in such patients.

We observed six patients with no TB history with positive IGRA results for 3 to 5 years, but none developed TB. In addition, both total conversion to negative results and fluctuations between results were observed.

Of the patients cases with no history of TB that became IGRA-positive during observation, two patients received prophylactic treatment with INH and later became IGRA-negative. The other two patients, observed with no treatment, also became IGRA-negative. For the 3 to 4 years following conversion to IGRA positivity, TB failed to appear in any of these four patients.

Of the 10 aforementioned IGRA-positive cases with no TB history, active TB did not occur over at least 3 years of observation in the eight patients who did not receive INH. It has been reported that repeated IGRA testing can produce variable results regardless of the presence or absence of infection risk, and that this can occur over relatively short time periods[8]. Our hospital confirmed this phenomenon with case fluctuations from positive to negative. The reasons for these fluctuations are unclear, though factors such as instability of test methods, variable interpretations of results, and immune system changes unrelated to infection are thought to play a role. Owing to these IGRA variations, uniformly administering INH to IGRA-positive patients in periodic testing may be premature. In the above cases, it is highly likely that immune function recovery (CD4 $\geqq 200\,\mu$/L) due to ART lowered the risk of developing active TB.

Among ELISPOT-positive cases with TB history at our hospital, three patients continued to test positive for 7 to 13 years, and four patients tested negative after 8 to 15 years. Clearly, it takes substantial time for ELISPOT to become negative in HIV/TB patients.

4. Examination of efavirenz and raltegravir plasma concentrations during rifampicin (RFP) administration

Rifampicin (RFP) induces cytochrome P450 in the liver, which accelerates the metabolism of a variety of drugs and reduces their plasma concentration, including that of key anti-HIV drugs. This phenomenon can make anti-HIV drug selection difficult. The nonnucleoside reverse transcriptase inhibitor efavirenz (EFV) or the integrase inhibitor raltegravir (RAL) are often selected, as these key drugs are not easily affected by RFP. An effect is still present, however, as the plasma concentration of both drugs were shown to decline when combined with RFP. Thus, it was thought the doses of both drugs need to be increased when combined with RFP, but the pharmacodynamics in Japanese patients have not yet been clarified.

To help clarify this phenomenon, we examined the achievement of optimal doses in patients who received EFV or RAL combined with RFP by measuring EFV and RAL plasma concentration[9]. Plasma concentrations of EFV and RAL were measured in 15 patients with HIV/TB. Patients received RFP combined with EFV or RAL at our hospital from 2001 to 2011. There were 14 men and one woman (14 received EFV and one received RAL) who received 600 to 800 mg/day of EFV. Blood samples were taken, on average, 13.7 hours after EFV administration. The median plasma concentration of EFV was 1,696 ng/mL (900−12,685 ng/mL), which was

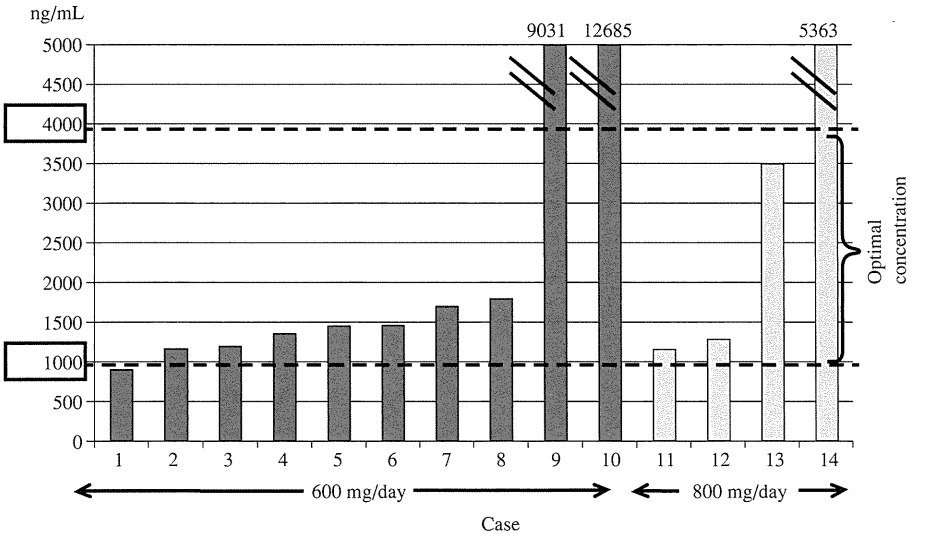

Fig. 4 Plasma concentration (trough) of efavirenz

above the target concentration of 1,000 ng/mL at 14 hours after administration (Fig. 4). Several patients exhibited extremely high plasma EFV concentration, and the dose was actually lowered to reach the optimal concentration. The patient who received RAL (1,600 mg/day) exhibited a trough plasma concentration of 26.6 ng/mL, well above RAL's IC95 of 14.5 ng/mL.

In general, RFP lowers the plasma concentration of anti-HIV drugs by inducing CYP3A4, but there are differences in this reaction across individuals. While EFV is mainly metabolized in the liver by CYP2B6, the gene has three genotypes (G/G, G/T, T/T). The T/T genotype is known to metabolize EFV slowly, which increases serum EFV concentration. However, none of the patients at our hospital had the T/T genotype.

Moreover, the neuropsychiatric symptoms that appear as a side effect of EFV are known to be dependent on plasma concentration. Thus, plasma concentration levels must be monitored to maintain the continuous administration that sustains the anti-HIV effect and suppresses side effects.

Conclusion

The author has researched HIV/TB since 1992. While HIV/TB cases are concentrated in large cities, it is doubtful that Japan's situation will lead to an immediate decline in the number of cases, prompting continued research to reduce HIV/TB incidence and improve prognosis.

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