STUDY

Low Blood Concentration of Hydroxychloroquine in Patients With Refractory Cutaneous Lupus Erythematosus

A French Multicenter Prospective Study

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Objective: To study the relation between blood concentration of hydroxychloroquine and the clinical efficacy of hydroxychloroquine sulfate in a series of patients with cutaneous lupus erythematosus (CLE).

Design: Prospective multicenter study. A staff dermatologist blinded to blood hydroxychloroquine concentrations performed a standardized review of medical records and assessment of hydroxychloroquine efficacy in the following 3 categories: complete remission, partial remission (clearing of >50% of skin lesions), or treatment failure. Whole-blood samples were collected for measurement of blood hydroxychloroquine concentration.

Setting: Fourteen French university hospitals.

Patients: Three hundred consecutive patients with subacute or chronic CLE who had been treated with hydroxychloroquine for at least 3 months.

Main Outcome Measures: The statistical significance of correlation between blood hydroxychloroquine concentration and efficacy of hydroxychloroquine and the statistical associations in univariate and multivariate analyses of complete remission with several variables.

Results: The study included 300 patients with discoid lupus erythematosus (n=160), subacute CLE (n=86), lupus erythematosus tumidus (n=52), chilblain lupus (n=26), and lupus panniculitis (n=16); 38 of these patients had 2 or more associated forms. Median blood hydroxychloroquine concentration was significantly higher in patients with complete remission (910 [range, <50 to 3057] ng/mL) compared with partial remission (692 [<50 to 2843] ng/mL) and treatment failure (569 [<50 to 2242] ng/mL) (P=.007). In the multivariate analysis, complete remission was associated with higher blood hydroxychloroquine concentrations (P=.005) and the absence of discoid lesions (P=.004). Thirty patients (10.0%) had very low blood hydroxychloroquine concentrations (<200 ng/mL) and may be considered nonadherent to the treatment regimen.

Conclusion: Monitoring hydroxychloroquine blood concentrations might improve the management of refractory CLE.

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ORAL ANTIMALARIAL AGENTS, most commonly hydroxychloroquine sulfate, are considered the first-line systemic treatment for cutaneous lupus erythematosus (CLE).[1] The prescribed hydroxychloroquine sulfate dosage theoretically depends on the patient's weight, with a maximal daily dose of 6.0 to 6.5 mg/kg adjusted to the ideal body weight (calculated in daily use as [body length in centimeters – 100] – 10% for men and [body length in centimeters– 100] – 15% for women).[2] Nonetheless, the standard daily dosage in France is frequently 2 tablets of hydroxychloroquine sulfate (ie, 400 mg/d), regardless of the patient's height and weight. The few studies that have addressed the pharmacokinetic variables underlying the management of hydroxychloroquine therapy in systemic diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE)[3-5] reveal great interindividual variability in blood hydroxychloroquine concentrations and thus raise the question of a relation between concentration and efficacy and of the utility of monitoring these concentrations. We have reported that a low blood hydroxychloroquine concentration is a marker of SLE activity and a predictor of lupus flares in patients with this disease and suggested a target blood hydroxychloroquine level of 1000 ng/mL for them.[5]

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To our knowledge, no studies have thus far reported blood hydroxychloroquine concentration data for patients with CLE. We therefore conducted a multicenter prospective study to evaluate this indicator in a large series of patients with CLE and to assess the relation between the clinical efficacy of the agent and the agent's blood level.

METHODS

PATIENTS

The multicenter study recruited consecutive patients from the departments of dermatology of 14 French university hospitals during an 18-month period. To qualify for enrollment in the study, patients had to receive hydroxychloroquine treatment for at least 3 months for chronic or subacute CLE. All patients were counseled on minimization of UV ray exposure and were prescribed sunscreens; if they had used topical immunomodulators or systemic immunosuppressive therapies during the 6 months before the study, they had maintained a consistent regimen and not stopped or started any such treatments. The local ethics committee approved the study protocol, which complied with French law and the rules of all participating institutions. Diagnoses of subacute CLE, discoid lupus erythematosus (DLE), lupus erythematosus tumidus, lupus panniculitis, and chilblain lupus were based on established clinical and histopathological criteria.[6]

A staff dermatologist at each hospital blinded to blood hydroxychloroquine concentration completed a case report form for each patient, including relevant data from the medical record and an assessment of hydroxychloroquine efficacy. The extracts included the type of CLE; the localization of the dermatologic lesions; the dates of the diagnosis of CLE and its first manifestations; disease duration; the type and number of American College of Rheumatology criteria for SLE[7]; the chronology, dosage, and efficacy of all treatments previously prescribed for CLE; the number of hydroxychloroquine tablets not taken during the preceding 4 weeks; smoking status (number of cigarettes smoked per day and pack-years for current and past smokers); alcohol consumption (past or current quantity of alcoholic drinks consumed per week); and the most recent laboratory test results, including C3 and C4 levels, the presence or absence of lupus anticoagulant, and measurement of antinuclear, anti–double-stranded DNA, anti–extractable nuclear antigen, anti-SSA (Ro 52-kDa and Ro 60-kDa), anti-SSB, anticardiolipin, and anti–β_2-glycoprotein 1 antibody levels.

Because the inclusion criteria included treatment with hydroxychloroquine for more than 3 months, all subjects can be presumed to have tolerated the treatment. Patients with adverse effects of the regimen that might interfere with treatment adherence were systematically excluded. Patients were considered to have SLE if they met 4 or more American College of Rheumatology criteria.[7]

Patients were classified in the following 3 groups according to their clinical status: complete remission (disappearance of all active cutaneous lesions), partial remission (clearing of >50% of skin lesions), or treatment failure (the remaining cases). Past damage from CLE was not considered.

Blood samples (10 mL) were collected in sterile vacuum tubes (Vacutainer; Becton, Dickinson and Company) containing 125 U of heparin each. The interval between the last ingestion of hydroxychloroquine and blood sampling was recorded. Because of the long terminal elimination half-life of hydroxychloroquine (>40 days), within- and between-day variations in blood hydroxychloroquine concentrations are small.[5] Accordingly, all blood hydroxychloroquine concentration data were retained for analysis regardless of the time from last ingestion to sampling. For maximum sensitivity and reproducibility, these concentrations were measured in whole blood[3-5] assayed using high-performance liquid chromatography with fluorometric detection as previously described.[5] The detection limit was 10 ng/mL, and the between-day and within-day coefficients of variation were greater than 8%. Blood hydroxychloroquine concentrations of less than 50 ng/mL could not be quantified.

STATISTICAL ANALYSIS

Statistical analysis was performed with commercially available software (SAS; SAS Institute, Inc). We used the χ^2 test and Fisher exact test when appropriate to compare nonordinal qualitative variables; a Wilcoxon or a Kruskal-Wallis test was used to compare ordinal or nonnormally distributed variables. Nonparametric correlations were tested with the Spearman test. Logistic regression and linear polynomial regression were used for multivariate analyses. We report medians and ranges for variables with a nongaussian distribution. Significance was defined by $P < .05$ in 2-tailed tests. We used univariate and multivariate analyses to examine the association of blood hydroxychloroquine concentration with the following variables: daily hydroxychloroquine dosage (stated in number of tablets, milligrams per kilogram, or milligrams per kilogram of ideal weight), body mass index, weight, height, smoking status (past or current tobacco use and number of cigarettes per day), and alcohol consumption. Univariate and multivariate analyses also investigated the correlations of complete remission with sex, type of CLE (subacute, discoid, tumidus, chilblain, or panniculitis), blood hydroxychloroquine concentration, presence of SLE, hydroxychloroquine dose (stated in milligrams per kilogram or in milligrams per kilogram of ideal weight), past or current smoking, and number of cigarettes per day. Unless otherwise indicated, data are expressed as median (range).

RESULTS

DESCRIPTION OF PATIENTS

This prospective study included 300 patients, of whom 253 (84.3%) were women and 47 (15.7%) were men. Diagnoses included subacute CLE (n=86), DLE (n=160), lupus erythematosus tumidus (n=52), lupus panniculitis (n=16), and chilblain lupus (n=26). Thirty-six patients had 2 different cutaneous subsets and 2 had 3 different cutaneous subsets. The **Table** summarizes the patients' characteristics according to sex. Age at study entry, number of current and ex-smokers, median number of cigarettes smoked per day (15.6 [range, 3-40] vs 11.2 [1-31]; $P=.005$), median number of pack-years (23.7 [1-60] vs 13.6 [1-40]; $P<.001$), and alcohol consumption were all higher in men. Women had detectable antinuclear antibodies (titer ≥1:320) and 4 or more American College of Rheumatology criteria for SLE more frequently than did men. The presence of 4 or more American College of Rheumatology criteria justified SLE diagnoses in 52 patients with DLE (32.5%), 41 (47.7%) with subacute CLE, 8 (30.8%) with chilblain lupus, 13 (25.0%) with lupus erythematosus tumidus, and 3 (18.8%) with lupus panniculitis. Patients with localized DLE had SLE less frequently than did patients with disseminated DLE (36 of 130 patients [27.7%] vs 15 of 30 [50.0%];

$P = .01$). Men with DLE constituted the group with the highest percentage of smokers (16 of 23 patients [69.6%]). As expected, 66 of 86 patients with subacute CLE (76.7%) had anti-SSA antibodies with equal distributions of Ro 52-kDa and 60-kDa antibodies (data not shown). Men reported missing hydroxychloroquine tablets in the past 4 weeks more frequently than did women (23.4% vs 9.5%; $P = .01$) and reported missing more tablets (mean, 1.1 vs 0.3; $P = .003$) (Table).

RESULTS OF BLOOD HYDROXYCHLOROQUINE CONCENTRATION

The median blood hydroxychloroquine concentration was 758 (range, <50 to 3057) ng/mL, significantly lower in men than in women (557 [<50 to 1572] vs 801 [<50 to 3057] ng/mL; $P = .007$). Median blood hydroxychloroquine concentration was significantly higher in patients with complete remission (910 [<50 to 3057] ng/mL) compared with partial remission (692 [<50 to 2843] ng/mL) and treatment failure (569 [<50 to 2242] ng/mL) ($P = .007$). The median blood hydroxychloroquine concentration was significantly lower in the 35 patients who reported missing hydroxychloroquine tablets than in other patients (606 [<50 to 1665] vs 830 [<50 to 3057] ng/mL; $P = .01$). Overall, 30 patients (10.0%) had blood hydroxychloroquine concentrations below 200 ng/mL and could be considered nonadherent to hydroxychloroquine treatment; these included 21 of 253 women (8.3%) and 9 of 47 men (19.1%; $P = .03$). Eight nonadherent patients were in the complete remission group, 8 in the partial remission group, and 14 in the treatment failure group. Nonadherent patients reported significantly more often than the others that they missed hydroxychloroquine intake (8 of 30 patients [26.7%] vs 32 of 270 [11.9%]; $P = .04$). They also missed more hydroxychloroquine tablets (1.6 vs 0.3; $P = .03$).

FACTORS ASSOCIATED WITH HYDROXYCHLOROQUINE CONCENTRATION AND COMPLETE REMISSION

In the univariate analysis of the entire group, hydroxychloroquine concentration was correlated with the hydroxychloroquine dosage stated in milligrams per kilogram ($P < .001$). It was inversely correlated with reporting missing hydroxychloroquine tablets ($P = .01$), body mass index ($P = .03$), and weight ($P = .003$). It was not correlated with the hydroxychloroquine dosage (expressed as the number of tablets or in milligrams per kilogram of ideal body weight) or with height, smoking, or alcohol use. In the multivariate analysis, the blood hydroxychloroquine concentration was correlated only with the hydroxychloroquine dosage (stated in milligrams per kilogram) ($P < .001$) and reporting missing tablets ($P = .008$). Blood hydroxychloroquine concentrations did not differ according to subtype of CLE (data not shown).

In the univariate analysis of the entire group, complete remission was negatively correlated with DLE (relative risk [RR], 0.57 [95% CI, 0.37-0.91]; $P = .02$) and male sex (RR, 0.38 [95% CI, 0.18-0.81] $P = .01$). Complete remission was positively correlated with the blood hydroxychloroquine concentration ($P = .007$). We found no correlation between complete remission and the daily dose of hydroxychloroquine, self-reported missing of tablets, body mass index, presence of SLE, cigarette smoking (total, past, or present or number of cigarettes per day), or alcohol consumption (data not shown).

In the multivariate analysis, the factors still associated with complete remission were a higher blood hydroxychloroquine concentration (RR for an increase of 1 ng/mL, 1.00073 [95% CI, 1.0002-1.156]; $P = .005$) and the absence of discoid lesions (RR, 0.48 [95% CI, 0.29-0.79]; $P = .004$). Therefore, a patient with a blood hydroxychloroquine concentration that was 200 ng/mL higher than the concentration of another patient was twice as likely to reach complete remission.

Table. Comparison of the Main Characteristics of Patients by Sex[a]

Characteristic	Women	Men	*P* Value
Sex	253 (84.3)	47 (15.7)	<.001
Age at the study, median (range), y	43.6 (12-85)	49.5 (16-79)	.009
Duration of skin lesions, median (range), y	2.4 (0.3-10)	2.6 (0.3-12)	.81
SLE (≥4 ACR criteria)	91 (36.0)	6 (12.8)	.001
Current smokers	97 (38.3)	27 (57.4)	.02
Past smokers	123 (48.6)	34 (72.3)	.004
Alcohol consumption >20 g/d	40 (15.8)	24 (51.1)	<.001
Detectable antinuclear antibody level (titer ≥1:320)	164 (64.8)	16 (34.0)	<.001
Anti-dsDNA antibodies	67 (26.5)	5 (10.6)	.60
Anti-SSA antibodies	97 (38.3)	8 (17.0)	.001
Antiphospholipid antibodies	35 (13.8)	6 (12.8)	.95
Hydroxychloroquine sulfate dose			
Prescribed 400 mg/d	215 (85.0)	34 (72.3)	.001
Prescribed dose, mean (range), mg/kg	6.6 (3.0-12.0)	5.4 (3.2-8.2)	<.001
Prescribed dose adjusted to ideal body weight, mean (range), mg/kg	7.2 (3.2-14.4)	6.3 (3.0-12.0)	.001
Patients who reported missing hydroxychloroquine tablets	24 (9.5)	11 (23.4)	.01
No. of missed hydroxychloroquine tablets, mean (SD)	0.3 (0.9)	1.1 (0.9)	.003
Clinical outcome status			
Complete remission	104 (41.1)	10 (21.3)	.02
Partial remission	68 (26.9)	18 (38.3)	.12
Treatment failure	81 (32.0)	19 (40.4)	.31

Abbreviations: ACR, American College of Rheumatology; dsDNA, double-stranded DNA; SLE, systemic lupus erythematosus.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

COMMENT

Our findings indicate that measurement of blood hydroxychloroquine concentration might be very useful in the management of CLE among patients receiving hydroxychloroquine treatment, especially those who are not responsive to the treatment. First, this assay made it possible to identify patients with poor adherence to treat-

ment, especially women, who were more likely than men to conceal from their physicians that they missed (intentionally or by forgetting) a hydroxychloroquine dose. Measuring adherence to a medication regimen is frequently difficult. Because of the long terminal elimination half-life (>40 days) of hydroxychloroquine, measuring blood hydroxychloroquine concentrations might be helpful for recognizing nonadherent patients. In this study, 10.0% of patients had very low blood hydroxychloroquine concentrations (<200 ng/mL) that were inconsistent with a regular hydroxychloroquine intake. A similar percentage of poor adherence to hydroxychloroquine treatment has been observed in SLE patients.[8] Recognition of nonadherent patients with CLE is very important because it is possible to conduct specific interventions to improve treatment adherence and thus avoid the prescription of more toxic drugs, such as thalidomide (used in France as second-line systemic therapy for refractory CLE). Similarly, hydroxychloroquine assays allowed detection of nonadherent patients with SLE. Intervention to improve their adherence to treatment may be useful to prevent SLE flares.[8]

Because a significant portion of hydroxychloroquine accumulates in several organs, especially melanin-containing retina and skin,[2] the skin concentration of hydroxychloroquine may differ quite substantially from the blood hydroxychloroquine concentration. Nevertheless, we observed a significant correlation between blood hydroxychloroquine concentration and hydroxychloroquine efficacy, and it persisted after exclusion of nonadherent patients and of patients who reported missing hydroxychloroquine tablets (data not shown). As emphasized by Wilkinson,[9] differences in drug response among patients are common, and these differences often make it difficult to optimize dosage regimens for individual patients.

This study did not allow us to evaluate the optimum blood hydroxychloroquine concentration range values for treatment of CLE. In patients with SLE, we have previously proposed 1000 ng/mL as the target blood hydroxychloroquine concentration.[5] Although a similar target is likely for CLE, prospective studies are required to determine this level more precisely. Cutaneous lupus erythematosus disappeared with increasing blood hydroxychloroquine concentration in some patients with low blood hydroxychloroquine concentrations in this assay (C.F., personal observation). This suggests, in our opinion, that hydroxychloroquine-refractory CLE cannot be diagnosed until skin lesions have persisted despite an adequate blood hydroxychloroquine concentration. We plan to conduct a prospective study to determine the percentage of patients with low blood hydroxychloroquine concentrations and persistent active CLE who achieve complete remission after their blood hydroxychloroquine concentration increases.

Increasing blood hydroxychloroquine concentrations might be associated with a higher incidence of adverse effects. We found no prior studies of this topic. Toxic retinopathy has previously been associated with higher doses and longer duration of use. It remains unclear, however, whether the critical factor was daily dose, duration of use, cumulative dose, or genetic susceptibility.[2,10] Recent data from a large cohort of 3995 patients show that toxic effects of hydroxychloroquine are associated with duration of therapy but not with daily dose or patient weight.[11] Moreover, in the revised recommendations of the American Academy of Ophthalmology on screening for chloroquine and hydroxychloroquine retinopathy, the risk of ocular toxic effects was considered to depend on cumulative exposure and be independent of the daily dose or the dose per kilogram of weight.[12] Although our study design did not assess toxic effects of hydroxychloroquine, inclusion required ongoing hydroxychloroquine treatment without retinopathy, which was tested regularly as recommended by the French Society of Ophthalmology.[13] Patients with other adverse effects of antimalarials that might interfere with treatment adherence were also systematically excluded.

We observed lower blood hydroxychloroquine concentrations in men than women, owing partially to poorer adherence to treatment by men (which they also admitted more easily). This finding also reflects the lower median prescribed hydroxychloroquine dose according to body weight in men (5.4 mg/kg) than in women (6.6 mg/kg; $P < .001$).

Hydroxychloroquine and chloroquine essentially do not accumulate in fatty tissues, and several authors[2] recommend modulating the hydroxychloroquine dose according to ideal body weight. This recommendation is not routinely followed in France given that 85.0% of the women and 72.3% of the men in our study had hydroxychloroquine prescribed at dosages of 400 mg/d. However, blood hydroxychloroquine concentration was strongly correlated in all groups to the daily dose stated in milligrams per kilogram but not to the daily dose stated in milligrams per kilogram of ideal body weight. If further studies confirm the correlation between blood hydroxychloroquine concentrations and drug efficacy in CLE, the adjustment of hydroxychloroquine dose to the ideal body weight should not be recommended.

Our data do not show that smoking has a direct effect on hydroxychloroquine metabolism. Blood hydroxychloroquine concentration was not related to smoking (present, past, number of cigarettes per day, or pack-years) in any of the subsets of CLE even after exclusion of nonadherent patients. Similar findings have been made in patients with connective tissue diseases.[14] Nevertheless, some reports suggest that smoking interferes with the effectiveness of antimalarial therapy in CLE.[15,16] Moreover, smoking has been reported to be a triggering factor for CLE,[17,18] although alcohol consumption is not.[17] In this study, we observed current cigarette smoking among a substantial proportion of patients with CLE (41.3%), especially in men with DLE (16 of 23 patients [69.6%]). The percentage of these men was nonetheless low (47 of 300 [15.7%]). The finding by Moghadam-Kia et al[19] that smoking is significantly more prevalent among patients with DLE that is considered refractory to various treatments suggests that the association of cigarette smoking and refractory DLE is not restricted to antimalarial therapy. Our study did not find a higher prevalence of smokers in patients with treatment failure than in those with complete remission (47 of 100 patients [47.0%] vs 55 of 114 [48.2%]). The high percentage of women in this study

(84.3%), known to smoke less than men, may explain why these data differ somewhat from the literature. Furthermore, this study included only patients referred to university hospital departments of dermatology who had more severe CLE. This setting probably induced some selection bias, which would explain some of the other anomalies in the characteristics of our study population. The female to male ratio was high, especially in patients with DLE (5.8); it is usually evaluated at about 2. The high prevalence of SLE was also unusual (36 of 130 patients with localized DLE [27.7%] and 15 of 30 patients with disseminated DLE [50.0%]), because the risk of developing SLE is estimated at only 5% for the localized form vs 20% for the generalized form.[6] However, none of these factors is likely to affect the blood hydroxychloroquine concentration and its relation to remission.

In multivariate analysis, the absence of DLE ($P=.004$) and higher blood hydroxychloroquine concentrations ($P=.005$) were the only factors significantly associated with complete remission of CLE. Accordingly, DLE, which is more frequently associated with cigarette smoking, appears to be more refractory to antimalarial therapy and probably to therapy with other drugs. The precise links between DLE and smoking and drug resistance are still poorly understood and require further studies. Cigarette smoke contains more than 100 toxic and carcinogenic substances that may have a direct deleterious effect on cutaneous lesions of lupus erythematosus. Immunomodulatory effects of cigarette smoking or common genetic backgrounds are other plausible explanations.[17]

The Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index is a new scoring system that has been developed to assess the severity of CLE, taking activity and damage into account.[20] It is a useful tool for double-blind, placebo-controlled, clinical trials. In this study, we did not use the activity score of the new index because our aim was not to score disease activity but rather to separate 3 groups of patients according to their response to antimalarials. Furthermore, all the subacute and chronic subtypes of CLE were included together.

It is often exceedingly difficult to treat CLE in patients who do not respond to antimalarials, and there is currently no satisfactory alternative treatment option. Thus, this study adds valuable and clinically relevant information about treating patients with CLE. Specifically, patients with CLE should not be considered to have disease that is refractory to hydroxychloroquine treatment before their whole-blood hydroxychloroquine concentration has been ascertained. Nonadherent patients, who are frequently in the treatment failure group (14 of 30 herein), can thus be identified before more toxic alternative treatments are administered.

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Notable Notes

Dermatogeographical Synonyms for Syphilis

Syphilis was identified by a geographical term representing a people, a city, or a nation in which skin diseases were misdiagnosed as syphilis.[1] Luca Landucci said that " . . . in 1496 [in Florence] there was a disease that was called *bolle franciose*. . . . " In 1498, Jacopo Manni, in his "Memoriale 1487-1530," wrote that the French spread the *vaiolo francioso* in Italy. At the end of 15th century, Antonio Benivieni[2] used the term *vaiolo spagnolo* for first time, and, later, Philip Barrough[3] used *variola gallica* in what is considered to be the first English publication about syphilis.

In the late 17th century, the adjectives *ispanico* or *ispano* were used to modify *vaiolo* or *vajolo* to describe syphilis. *Spaansche pooken*, *spaanses pocken* (where *pocken* means pox), and *French pox* were also used to describe syphilis.[4] Some European chroniclers called syphilis *vaiolo di Spagna* and attributed the spread in Africa to the Marrani (Hebrews) when they were driven out of Spain in 1492.[5] Pietro Parvo Rosaefontano[6] wrote in his "Chronicon Johannis Regis Daniae" that King John of Denmark said " . . . during the summer [in 1495] a very great contagious disease commonly called *scabbia gallica* was known . . . ." This synonym, *scabbia gallica*, was still used in a Venitian hospital in 1789.[7] Antonio Benivieni[2] wrote the following regarding New World disease: " . . . [In] America [some] poxes similar to scabbia gallica were present . . . ." Piero Di Marco Parenti[8] used the term *rogna franciosa* for syphilis, while Pietro Rostino[9] used *rogna gallica*. Other authors called syphilis *rogna francese*, *scabbia francese*, and *scabbia mala franzosa*. The synonyms *scabia ispanica*, *scabie spagnola*, and *sarna espagnola* (*sarna* means scabies in Spanish) originate from the Spaniards, who spread syphilis from Indies. Syphilis was also called *scabbia indica*.

In recognition of the Old Testament plagues imposed by God onto the Egyptians, Francisco Lopez de Villalobos used the term *scabbia d'Egitto* to describe syphilis. Because the sixth plague is the plague of the ulcer, syphilis became the *piaga egizia, plaga egipciaca*, and *piaga egiziaca*. In the final years of the 15th century, European scholars called syphilis *carbunculum Franciae* and *piaghe franciose*. Finally, in the 16th century, Europeans saw syphilis as the Black Death and named it *peste di Bordeaux*, *peste celtica*, or *peste marranica*.

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