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PLASMA CONCENTRATIONS OF GRISEOFULVIN IN HEALTHY VOLUNTEERS AND OUT-PATIENTS TREATED FOR ONYCHOMYCOSIS

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Abstract. Therapeutic failures of griseofulvin therapy are fairly common, especially when toe nail infections are treated. The reasons for the failures remain largely unknown. The aim of the present investigation was to study whether pharmacokinetic factors may be responsible. At first, single-dose and steady-state pharmacokinetics of griseofulvin were analysed in volunteers by means of a gas-chromatographic technique. It was found that there was no difference in plasma levels of the three brands of griseofulvin commercially available in Sweden, whereas there was a significant difference of absorption between individuals. The plasma half-life varied considerably from day to day in the same individual. In the second part of the investigation griseofulvin plasma concentrations were determined in 27 patients treated with griseofulvin for onychomycosis and related to the therapeutic result. All patients but one were initially improved but the therapeutic effect faded in 15 patients after 5–20 months of treatment ("partially healed" patients). In 11 patients the nail infections were clinically healed after 6–24 months. However, no statistically significant difference of the plasma griseofulvin levels could be demonstrated between the healed and partially healed groups. Some possible reasons for the therapeutic failures are discussed.

Key words: Griseofulvin; Pharmacokinetics; Onychomycosis

Before the introduction of griseofulvin for clinical use in 1958, dermatophyte infections of nails were virtually incurable. However, the initial enthusiasm for the drug soon diminished as it was realized that both therapeutic failures and relapses were fairly common (6, 9, 11, 23, 29). The factors responsible for the failures are still largely unexplained. Appearance of insensitive fungal strains seems to be a very unlikely cause of lack of response (6, 7, 21) although increased resistance of the fungi to griseofulvin has been demonstrated (13, 17, 18, 25).

Unsuccessful results may also be due to inadequate dosage, poor absorption (1, 13) or rapid elimination, all producing insufficient concentrations of the drug in plasma and tissues. This possibility could be checked by determining the plasma levels of griseofulvin in patients treated for fungal infections and then relating the plasma concentrations to the clinical result of the drug treatment in each individual. This has been attempted in the present study of out-patients at a dermatology department. For comparison, single dose and steady-state pharmacokinetics have also been analysed in volunteers where the conditions during administration could be more closely controlled.

MATERIAL AND METHODS

Single dose studies in volunteers

Six healthy volunteers, 3 males and 3 females, aged 24–40 years, participated. None of them had any other medication. Five hundred mg griseofulvin was taken orally in the morning 1–2 hours after a light breakfast. No food was allowed within the first 4 hours following the administration. Three different brands of griseofulvin (see below) were taken in this way by each volunteer on three different occasions with a minimum interval of one week. Blood sampling was performed for at least 24 hours after each dose.

Steady state studies in volunteers

Four of the above subjects, 3 males and 1 female, also took part in a study with a daily dose of 500 mg griseofulvin (Fulcin®) during 8 to 10 days. The dose was taken orally every evening and blood samples were taken on the following mornings and afternoons.

Patient study

In the clinical part of the investigation all out-patients were included who were treated with griseofulvin for

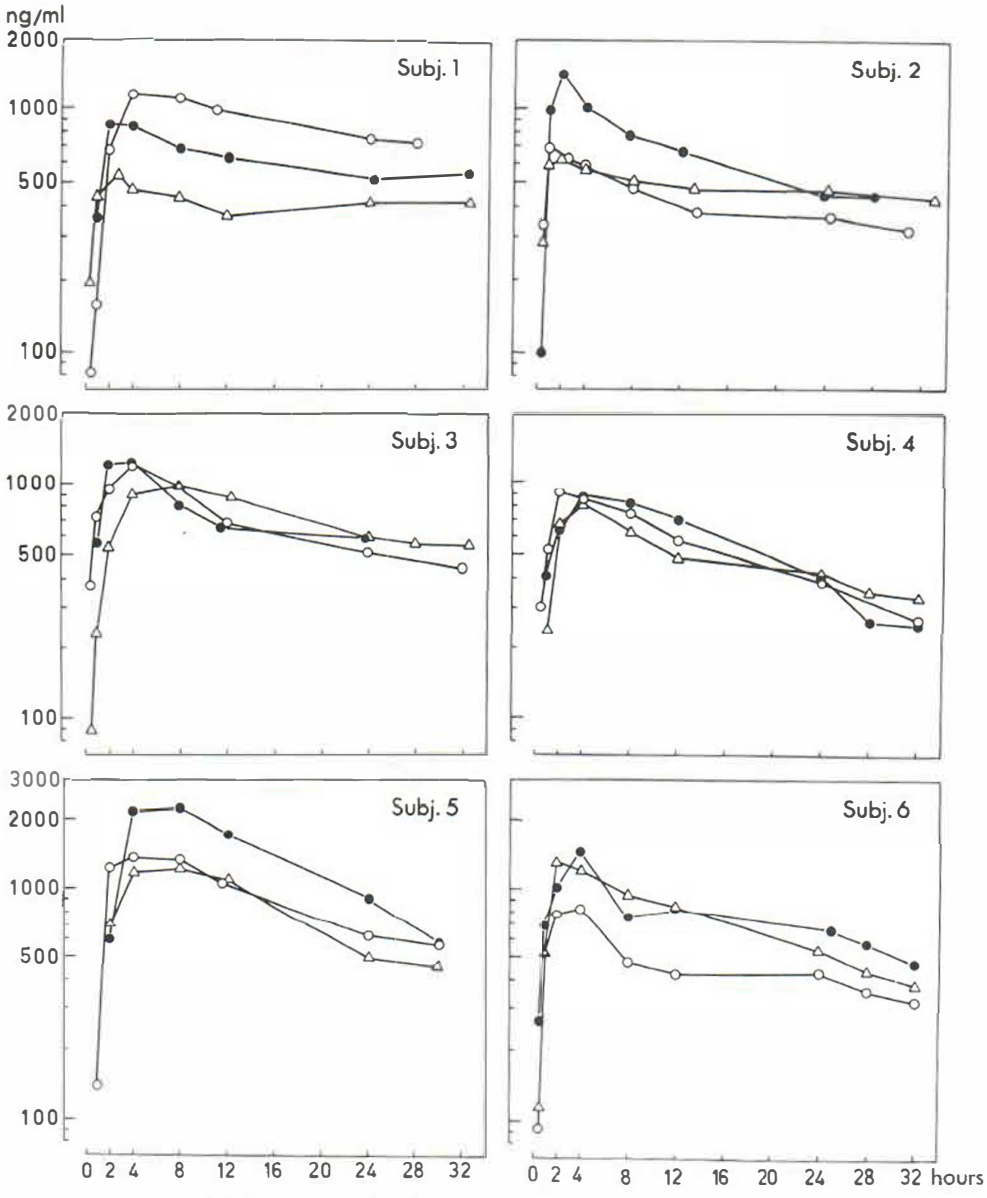

Fig. 1 Plasma griseofulvin concentrations in 6 volunteers after a single oral dose (500 mg) of Fulcin (△), Grisovin (○) and Lamoryl (●).

onychomycosis and who attended the dermatological department during a period of one year. Either griseofulvin therapy had been started previously or was begun during this period. After exclusion of those patients who had been on treatment for more than one year before this investigation started, 32 patients remained. However, 4 of them did not return for regular examinations, and 1 stopped griseofulvin intake after one month because of diarrhoea. Thus, the relation between clinical effect and serum concentration of griseofulvin could be determined in 27 patients, 16 males and 11 females, aged 15 to 60 years at the onset of the investigation.

In all patients the diagnosis had been confirmed by culture before griseofulvin therapy was started. Twenty-six cases had toe-nail infections and 4 of these patients had infected finger nails as well. In one case finger nails alone were infected. The most common fungus species was *Trichophyton rubrum* which was found in culture from 22 patients. Other dermatophytes cultured were: *Trichophyton mentagrophytes* in 3, *Microsporon gypseum* in 1

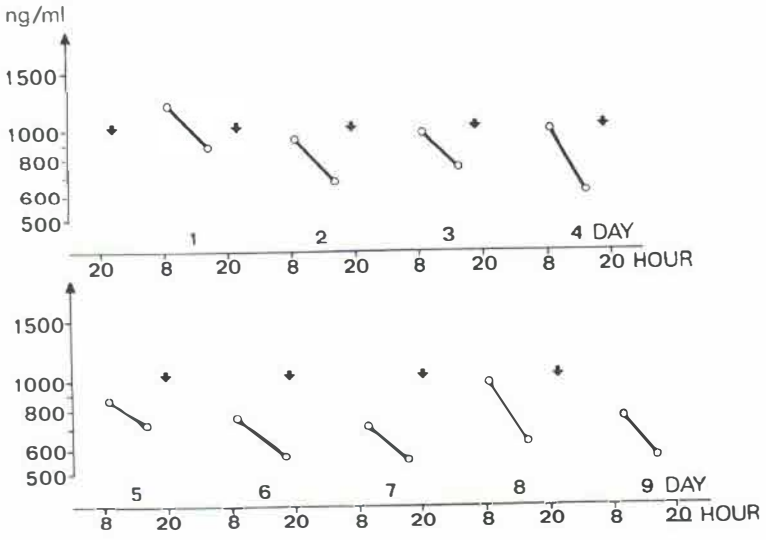

Fig. 2. Plasma concentration values in one of the volunteers taking griseofulvin (Fulcin) orally for 9 days. Each arrow denotes administration of a 500 mg dose.

and *Epidermophyton floccosum* in 1 patient. Clinically the infections belonged to the class of "distal subungual onychomycosis" described by Zaias (30).

A photograph of the nails was taken at the first visit, and a schematic drawing of the nails with their lesions was made at each examination. The distance from the proximal nail fold to the nail lesion was measured. The condition was considered improved when the distance from the proximal nail fold to the lesion had increased. The patients were examined at intervals of 2–4 months. All patients were followed for at least 12 months or until the lesions had disappearaed.

Treatment started with griseofulvin 0.5 g once a day. No concomitant topical treatment was given. On each visit to the dermatological department a single capillary blood sample for griseofulvin analysis was taken. The patient was instructed to take his griseofulvin tablet at such time on the previous evening that the interval between administration and blood sampling was 17±1 hours.

Griseofulvin analysis

Capillary blood was collected in heparinized hematocrit tubes. The samples were stored at +4°C for less than 8 hours before centrifugation. Plasma was kept frozen until analysis. Griseofulvin was determined by gas chromatography according to the principles described for analysis of diazepam (3), where griseofulvin is used as the internal standard. The following modifications were made: 100 µl of plasma was extracted with 1.00 ml toluene containing *N*-desmethyl-diazepam 600 ng/ml. No evaporation was needed and 2–4 µl of the extract was analysed direct by gas chromatography. A Varian 1400 gas chromatograph equipped with a ^{63}Ni-detector was used. The column was packed with OV-17 3 % on Gas Chrom Q 80–100 mesh. The nitrogen flow rate was 30 ml/min and the temperature in the column 275°C. A standard curve was prepared by subjecting plasma samples with known concentrations of griseofulvin to the procedure described and plotting the peakheight ratio between griseofulvin and *N*-desmethyldiazepam against the concentration of griseofulvin added/ml serum. The method can be used down to 30 ng/ml without evaporation of the solvent. The standard deviation was 7, 4, and 5 % of the mean value at concentration ranges of 250–500, 750–1 000, and 1 250–1 500 ng/ml griseofulvin, respectively.

Drugs

The three brands of griseofulvin commercially available in Sweden were used: Fulcin (ICI), Grisovin (Glaxo) and Lamoryl (Lövens) 125 mg tablets. In the patient study 500 mg tablets of Fulcin were used.

RESULTS

Single dose studies in volunteers

This part of the study was organized as a cross-over experiment with three brands of griseofulvin tablets taken on three different occasions by each of the 6 volunteers. The resulting plasma levels are demonstrated in Fig. 1. In all cases there was a rapid absorption of the drug with peak values (mean±S.D. 1 219±459 ng/ml) at 2–4 hours after administration. The area under the plasma concentration curve (AUC) for the first 24 hours was determined in each case. The 18 AUC values thus obtained were subjected to an analysis of variance which showed a significant variance between subjects ($p<0.05$) but not between drugs ($p>0.05$).

Steady-state studies in volunteers

The plasma concentration values in one of the 4 volunteers, taking griseofulvin during 9 days, are

Table I. *Steady-state studies in volunteers*

Day-to-day variation in rate of disposition of griseofulvin, calculated on the basis on two plasma samples per slope and expressed as half-lives ($T_{\frac{1}{2}}$) and elimination rate constant (K_e). The final slope was determined on the basis of 5–10 samples. Dose: 0.5 g griseofulvin (Fulcin®) per day

	Subject 1		Subject 2		Subject 3		Subject 4	
	$T_{\frac{1}{2}}$ (hours)	K_e (hours^{-1})	$T_{\frac{1}{2}}$ (hours)	K_e (hours^{-1})	$T_{\frac{1}{2}}$ (hours)	K_e (hours^{-1})	$T_{\frac{1}{2}}$ (hours)	K_e (hours^{-1})
Day 1	33.4	0.0208	17.9	0.0387	12.1	0.0573	6.4	0.1083
Day 2	22.8	0.0304	17.9	0.0387	17.2	0.0403	9.0	0.0770
Day 3	20.9	0.0332	17.9	0.0387	22.9	0.0303	10.6	0.0654
Day 4	13.9	0.0499	10.0	0.0693			22.3	0.0311
Day 5	12.9	0.0537	28.3	0.0245	11.0	0.0630	9.4	0.0737
Day 6	9.3	0.0745	21.5	0.0322			25.5[a]	0.0272
Day 7	12.2	0.0568	27.4	0.0253			9.5[a]	0.0729
Day 8	11.1	0.0624	12.0	0.0578				
Day 9			14.3	0.0485				
Final slope	33.4	0.0208	21.9	0.0316	25.3	0.0274	11.0	0.0630
	$r=0.99$ $n=10$		$r=0.99$ $n=7$		$r=0.95$ $n=8$		$r=0.98$ $n=5$	

[a] Dose 1 g/day.

shown in Fig. 2 and the day-to-day variation in half-lives for all subjects is given in Table I. It is obvious that the decay between morning and afternoon values of each dose cycle shows considerable day-to-day variations. The concentration at 17 hours after each administration was arbitrarily taken as a measure of the daily level and was selected since it allowed comparison with the values from the patient study. The 17-hour values (mean±S.D.) for the 4 volunteers were 850±224, 729±157, 859±51 and 778±324 ng/ml, respectively.

Patient study

Data and results from the patients are summarized in Table II. In the beginning all 27 patients but one were improved, i.e. the infected distal part of the nail moved outwards and the proximal healed part increased in size. However, after 5–20 months' treatment this effect ceased in 15 patients and there was no further improvement. In the following this group is called "partially healed". In 11 patients the toe nail infections were clinically healed after 6–24 months.

The plasma levels determined 17±1 hours after griseofulvin administration showed no statistically significant difference ($p>0.05$) between the healed and partially healed groups, 751±355 and 595±172 ng/ml, respectively (mean±S.D.).

In some of the partially healed patients the griseofulvin dose was doubled to 1 g once a day (patients 17–27). This led to healing in 2 cases, partial healing in 3 cases and no further response in 5 cases (Table III). The griseofulvin therapy was then withdrawn, except in 2 patients who received 1 g b.i.d. but without further improvement.

The plasma levels in those who were partially healed did not decrease during treatment, i.e. the stagnation of the therapeutic effect was not associated with decreased plasma concentrations of griseofulvin.

In a few patients the growth of the nails was followed by making a notch in the nail plate. In one patient in whom both finger and toe nails were observed it was found that the finger nails grew twice as fast as the toe nails. Even in those patients who responsed well to therapy the notch moved outwards faster than the infected lesion.

No serious side effects were noted during this investigation except for the patient who stopped drug intake because of diarrhoea. A few patients complained of headache. No drug eruption or photodermatitis was observed.

DISCUSSION

Griseofulvin has been the subject of several pharmacokinetic studies (2, 4, 5, 8, 14, 15, 22, 24, 27, 28) but no investigator has tried to correlate plasma levels in patients under treatment to the clinical effects of the drug. In the present paper an attempt has been made to do this in patients with onychomycosis. The

Table II. *Summary of data from the 27 patients*

Griseofulvin dose: 0.5 daily. Plasma griseofulvin conc. determined 17±1 hours after the last griseofulvin administration. F=fingers, T=toes, TR=Trichophyton rubrum, TMG=Trichophyton mentagrophytes var. granulosum, MG=Microsporon gypseum, EF=Epidermophyton floccosum

								Healed			Partially healed			No response		
Pat. no.	Sex	Age (y.)	Site of nail infection F	T	Fungus	Growth rate of nails (μm/day) F	T	Plasma conc. (ng/ml) M±S.D.	n	Duration of treatment (mo.)	Plasma conc. (ng/ml) M±S.D.	n	Duration of treatment (mo.)	Plasma conc. (ng/ml) M±S.D.	n	Duration of treatment (mo.)
1	♂	55	F+	T	TR		50	628±203	6	18[a]						
2	♂	51	F+	T	TMG			454± 46	6	15[b]						
3	♀	61		T	TR			517±175	4	19						
4	♀	51		T	TR			689±219	3	24						
5	♂	15		T	TR			771±188	3	14						
6	♂	30		T	TR			771	2	6						
7	♂	48		T	TR			907	2	14						
8	♀	60	F		TR			555	2	(8[c])						
9	♀	39		T	TR		64	491± 39	3	24						
10	♀	53		T	TMG		59	743±146	6	18						
11	♂	57		T	MG			1 733±446	4	21						
12	♂	32		T	TR		65				546	2	13			
13	♀	47		T	TR		89				688±127	5	18			
14	♂	55		T	TR						845±138	4	18			
15	♂	60		T	TR		58				583±141	4	20			
16	♂	58		T	TMG						528±143	5	13			
17	♀	53		T	TR						642±198	3	19			
18	♀	60		T	TR						961	2	5			
19	♀	24		T	TR						Not determined[d]		6			
20	♂	52		T	TR		61				Not determined[d]		12			
21	♂	47	F+	T	TR	163	82				343	2	6[d]			
22	♂	47	F+	T	TR		54				575± 90	3	12[e]			
23	♂	56		T	TR		106				436	2	7			
24	♂	57		T	TR						375± 52	5	10			
25	♀	61		T	TR						631	1	16			
26	♂	54		T	TR						582±112	4	11			
27	♀	31		T	EF									405	1	8
Mean±S.D.							69±18	751±355		17.3±5.4	595±172		12.4±5.0	405		8
n							10	11		10	13		15	1		

[a] Finger nails healed in 6 months.
[b] Finger nails healed in 15 months.
[c] Finger nails healed in 8 months (figure not included in calculation of mean healing time).
[d] Finger nails healed in 12 months.
[e] Finger nails healed in 22 months.

purpose was to find out if such a correlation could be demonstrated in an unselected group of out-patients treated with a standard dose of griseofulvin. If so, a system with routine determination of plasma levels would be a way to optimize the dosage and thereby to improve the therapy.

Since some differences in bioavailability between the marketed brands of griseofulvin could not be ruled out, a cross-over study in 6 volunteers was performed first. All the three products tested were of the micronized type and all gave peak plasma values within 2-4 hours following administration. The analysis of variance for the area under the plasma concentration curve during the first 24 hours demonstrated a significant variance between the 6 subjects but not between the three brands. Thus, any of the available preparations could have been used for the subsequent patient study but Fulcin was selected because of local tradition at the dermatological department.

Before the patient study was designed, some background information was also needed on the variation in plasma levels during repeated administration of griseofulvin. Thus, Fulcin was taken by 4 volunteers during a 10-day period. In order to mimic the patient situation, no special food restrictions

Table III. *Griseofulvin plasma concentrations determined 17±1 hours after the last griseofulvin administration in the patients where griseofulvin dose was raised to 1 g and 2 g daily*

	Griseofulvin 1 g once daily								Griseofulvin 1 g b.i.d.		
	Healed			Partially healed			No response		No response		
Patient no.	Plasma conc. (ng/ml) M±S.D.	n	Cumulated duration of treatment (mo.)	Plasma conc. (ng/ml) M±S.D.	n	Cumulated duration of treatment (mo.)	Plasma conc. (ng/ml) M±S.D.	n	Cumulated duration of treatment (mo.)	Plasma conc. (ng/ml) M±S.D.	n	Cumulated duration of treatment (mo.)
17				781±144	3	30						
18	1 228±139	5	23									
19	851	2	19									
20				1 312	1	22				1 313		26
21				463	1	12						
22							481	1	15	867±304	3	24
23							785	2	13			
24							652	1	16			
25							984	1	19			
26							1 189	1	14			
27							795	1	11			
Mean ±S.D.	1 040		21	853±429		20.3±7.6	814±248		14.7±2.7	1 090		25
n	2		2	3			6		6	2		2

were observed. Two daily plasma determinations were made, both during the declining part of the log concentration-time disposition curve (according to the results of the cross-over study). Such a simplified sampling protocol was sufficient to give an estimate of the degree of variation to be expected in the subsequent patient study. It showed that there was no tendency towards a continuous increase or decrease in the plasma levels with time over the 10-day period. The same was true for the disposition rate constants (or half-lives). The post-steady state slopes (final slopes) were similar to those during the observation period. The 17-hour-after-dose value was selected as a reference point in the patient study where, for practical reasons, only one single determination was possible.

The results of the treatment were generally good. In 11 of the 27 treated patients the nail infections were clinically healed, i.e. they were either completely cured or there was only a very slight remaining ruggedness at the outermost fringe of the nail along with a negative dermatophyte culture. Davies et al. (6) observed that only 1 patient of 66 with *T. rubrum* infections of the toe nails was clinically cured. The reason for this discrepancy is not clear. One difference is that Davies et al. did not use the micronized type of griseofulvin which is known to be better absorbed from the gastrointestinal tract (5).

It is interesting that most patients who could not ultimately be classified as healed, showed an initial response to the therapy with a stagnation after 5–20 months of treatment. This phenomenon has been reported earlier by others. Frydrychowics (9) found that all nail lesions improved initially but after 5 months in some patients the border between the proximal healed part and the distal infected part did not move any further. Meinhof (21) also noted that in many patients the therapeutic effect faded but he also found that increased resistance of the fungi was not the reason. Another explanation for the disappearance of the therapeutic effect would be an enhanced rate of metabolism and/or excretion of the drug leading to a fall in the plasma levels. However, our plasma data give no support for this theory. An alternative possibility would be poor compliance of patients with the prescribed dose after some time. However, this does not seem to be likely since the patients were well motivated to the treatment and the drug was virtually free from side effects.

We found that the nail plate moved outwards at a faster rate than the infected lesion even in the patients who responded well to therapy. The same was found by Grimmer (12) who proposed that when the nail plate is sliding over the nail bed it is dragging the mainly subungual lesion behind it like "a glacier on a mountain".

It is evident from the present study that there is no clear-cut correlation between the clinical result of

treatment and the plasma level of griseofulvin as determined at the time of visit to the dermatological out-patient department. The "healed" patients had a higher mean plasma concentration at 17 hours after dose than the "partially healed" patients but the difference is not statistically significant. A single value on the concentration curve during a dose cycle may not be enough to characterize the total exposure of the target organ to a drug like griseofulvin with its rapid elimination from the blood and its well-known variation in absorption when the food intake is not controlled. From the pharmacokinetic point of view, the ideal situation would be to determine, by taking many blood samples during one dose interval, the area under the plasma concentration curve (as we did in our cross-over experiment) and correlate it to the clinical results. However, this is not feasible as a routine in out-patients.

Even if such a close surveillance of the plasma concentrations in our patients had been possible, a simple correlation to the clinical effect should not have been expected, since the drug concentration at the target organ, i.e. the nails, should be the determining factor for the interaction with the fungus. It has been assumed that griseofulvin is somehow metabolically incorporated in the keratin of skin (26) or hair (10). On the other hand, it has recently been found that griseofulvin can be recovered in the corneal layer of skin even a few hours after administration (8, 28). In contrast to previous reports it has also been found that a topical application of griseofulvin can be used for treating ring worm infections when griseofulvin is dissolved in DMSO or DMAC (16, 19). These recent observations indicate that griseofulvin may not "have to grow with the keratinocytes" but may be transported to the keratinous material by sweat secretion or diffusion.

to penetrate the nail plate from underneath, i.e. from the nail bed, to reach the infection sites. If this is true, the most distal part of the nail plate not in direct contact with underlaying tissues, may obtain lower concentrations of griseofulvin. This in turn may explain why in some cases the free distal end of the nails did not become free of infection, although all the proximal part of the nail overlying the nail bed was clinically cured.

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