What is the appropriate duration of a therapeutic trial in cutaneous tuberculosis? Further observations

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ABSTRACT

Background: Laboratory tests for the diagnosis of cutaneous tuberculosis lack adequate sensitivity and specificity and a trial of therapy is often used as a diagnostic test in difficult cases. However, the duration for which the trial should be undertaken is not clearly defined. Our previous study indicated that one month of therapy was adequate to detect a clinical response to treatment. However, about half the patients first reported after one month of treatment, some much later. **Method:** We therefore analysed the treatment records of 107 patients who received four-drug, short course, antitubercular therapy for a diagnosis of cutaneous tuberculosis in our hospital and who were asked to return for follow-up at biweekly intervals in the first month of treatment. **Result:** Twenty-one patients did not return for any follow-up visit, nine patients did not respond to treatment and treatment was stopped in one patient. Of the remaining 76 patients, 72 patients were recorded to have distinct clinical improvement within five weeks of starting treatment while only four patients showed improvement after 60-123 (8-17 weeks) days of therapy. **Conclusion:** These findings indicate that five weeks appears to be an adequate duration of a therapeutic trial in patients suspected to have cutaneous tuberculosis, with the exception of tuberculids and patients showing minimal clinical activity before treatment. Patients who have not responded by this time are unlikely to do so with further treatment and should have their diagnosis reviewed.

Keywords: Diagnosis, Lupus vulgaris, Scrofuloderma

The laboratory diagnosis of cutaneous tuberculosis is difficult. Microbiological tests such as direct microscopy and culture are usually negative in cutaneous tuberculosis because it is paucibacillary.[1-7] Histopathological findings are characteristic but not pathognomonic and are shared by other granulomatous diseases including leprosy, sarcoidosis, leishmaniasis and subcutaneous fungal infections. There is conflicting evidence of the utility of polymerase chain reaction (PCR) as a diagnostic test.[8-12] Consequently, a therapeutic trial is often undertaken in difficult cases of suspected cutaneous tuberculosis to resolve diagnostic confusion. While the need for a therapeutic trial is recognized,[13] there are no guidelines on how long to treat a patient before deciding that a trial has been successful or has failed and should be abandoned.

In practice, patients often receive treatment with multiple drugs and for long durations exceeding the standard period of therapy before the diagnosis is reconsidered. A previous study of the records of patients treated at our hospital indicated that most patients who eventually responded to treatment began to do so within a month of starting therapy.[14] However, in that study, about half the patients reported for the first follow-up visit more than one month after therapy and we could not be certain that improvement had begun during the first month. Subsequently, we changed the follow-up protocol in our patients and they were asked to report every 2 weeks in the first month and then once every month. We report the findings in this group of patients who were followed up more frequently after initiating treatment.

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METHODS

The study consisted of patients attending the skin outpatient department (OPD) in our hospital between June 2000 and February 2003. All patients who were clinically suspected to have cutaneous tuberculosis were evaluated. Skin biopsy, Mantoux test, chest X-ray, hemogram and serum biochemistry were performed in these patients. Other tests including fine needle aspiration cytology, lymph node biopsy and radiological imaging were conducted when clinically indicated. If the diagnosis of cutaneous tuberculosis was sustained by clinical and laboratory testing, patients were prescribed therapy.

Antitubercular therapy consisted of isoniazid 300 mg daily, rifampicin 450 mg daily, ethambutol 800 mg daily and pyrazinamide 1500 mg daily for two months followed by isoniazid and rifampicin in the same doses for four months. The doses were suitably adjusted for children. Patients who had tuberculosis of the bone were treated for 18 months. In one patient with nephritic syndrome, rifampicin was substituted by sparfloxacin. Patients were asked to return for follow-up visits at biweekly intervals in the first month of starting therapy and once a month till the end of treatment. If a patient came late for his appointment, he was not excluded from the study; his improvement and the time of the visit were recorded.

If a patient sought consultation apart from his scheduled follow-up visit for any reason, the improvement in the skin lesion at the unscheduled visit was also recorded. A dermatologist examined the patient at every visit. Patients who had plaques and papules were evaluated for a reduction in induration, scaling, verrucosity and erythema while patients with sinuses, ulcers and discharge were assessed for a reduction in discharge and healing of the sinuses or ulcers. For each patient, we noted the number of days of therapy after which distinct, clinically perceptible improvement had been recorded.

RESULTS

A clinical diagnosis of cutaneous tuberculosis was considered at initial evaluation in 130 patients. The diagnosis was excluded on clinical and / or laboratory testing in 23 patients. In the remaining 107 patients, the diagnosis was considered likely enough to recommend antitubercular therapy. There were 50 females and 57 males, aged 3-60 (median 23 years, mean ± SD = 24.9 ± 13.28 years). The clinical diagnoses were lupus vulgaris in 54 patients, scrofuloderma in 34, scrofuloderma and lupus vulgaris in one, tuberculosis verrucosa cutis in six, lichen scrofulosorum in eight and erythema induratum in four. The median duration of disease was 1.25 years (range 15 days to 35 years) (mean 2.84 ± 0.42 years).

Mantoux test was performed with 5 Tuberculin units (TU) of purified protein derivative (PPD) (Span Diagnostics) in 95 patients. When read at 48 hours, induration of 10-44 mm was found in 49 patients while induration was absent in 38 patients and ranged from 4-9 mm in the remaining eight patients. Skin biopsy was performed in 98 patients and showed histopathological features compatible with cutaneous tuberculosis in 87 patients; the features were nonspecific in the remaining 11 patients. Radiological investigations revealed pulmonary tuberculosis in 12 patients (two of whom also had tuberculosis of the bone), tuberculosis of the spine in one patient and a parietal tuberculoma of the brain in one patient. Aspiration cytology or biopsy showed tuberculosis of the lymph node in six other patients.

Response to therapy

Twenty-one patients did not return for a single follow-up visit after they were advised therapy. Nine patients did not respond to therapy. One patient suspected to have lichen scrofulosorum showed clinical benefit after 60 days of therapy. However, re-evaluation at three months revealed that he had lichen nitidus and his treatment was stopped. Seventy-six patients were recorded to show distinct clinical improvement in response to therapy. The number of days for which therapy was received by each patient at this end-point was five days (one patient), six days (1), seven days (11), eight days (1), ten days (3), 11 days (1), 12 days (7), 13 days (3), 14 days (11), 15 days (3), 16 days (2), 17 days (3), 19 days (3), 20 days (4), 21 days (1), 22 days (5), 26 days (3), 27 days (1), 28 days (4), 31 days (2), 35 days (2), 60 days (1), 62 days (1), 88 days (1) and 123 days (1).

Early responders

Seventy-two patients showed distinct clinical improvement after receiving ≤ 35 days of treatment.

Slow responders

Four patients showed distinct clinical improvement after 60-123 days of therapy. Two of these patients had lesions on the breast with scarring, minimal discharge and slightly elevated plaques and showed distinct clinical improvement after two and four months of therapy respectively. New papules of lichen scrofulosorum continued to develop in one patient even after two months of therapy after which they

healed completely. Another patient with erythema induratum showed healing of nodules after 88 days of treatment.

Non-responders

Nine patients did not respond to antitubercular therapy. The diagnosis was incorrect in four patients. One patient with suspected lupus vulgaris did not respond to one month of therapy; she was found to have sporotrichosis and treated with potassium iodide to which she began responding within 11 days and her condition cleared in two months. One patient with a diagnosis of scrofuloderma / dental sinus received treatment for two months with no improvement. However, following dental extraction and antibiotic therapy, the sinus healed completely. One patient with a diagnosis of scrofuloderma received treatment for two months with no improvement. She was subsequently diagnosed with hidradenitis suppurativa and treated with isotretinoin with which there was partial improvement.

One patient with suspected lupus vulgaris worsened within ten days of treatment; pyoderma gangrenosum was diagnosed and he was treated with corticosteroids with which the lesions healed in one month. The duration of treatment and follow-up was short in two patients. One patient with a diagnosis of erythema induratum followed up for 14 days deteriorated and was subsequently lost to follow-up. One patient with lupus vulgaris followed up for 14 days without a response and was also subsequently lost to follow-up. No cause of lack of response was found in three patients. One patient with a diagnosis of lupus vulgaris received treatment for six months with no response. He was evaluated for the presence of fungal infection and was treated empirically with potassium iodide and itraconazole with no response. Finally, he underwent cryotherapy following which the lesion was ablated and has not recurred.

One patient with a diagnosis of scrofuloderma received treatment for one month, deteriorated during therapy and was subsequently lost to follow-up. One patient with lupus vulgaris overlying scrofuloderma showed no improvement in 60 days; she was treated subsequently with itraconazole therapy leading to improvement. Fifty-six patients followed up till complete remission which was defined as the absence of clinical signs of disease activity (erythema, induration, scaling, verrucosity, sinuses, ulcers and discharge) which was recorded after a mean duration of 114.2 days (± 70.2) (median 93, range 21-455 days). About 42 patients followed up till the therapy was completed.

DISCUSSION

The vast majority of our patients with cutaneous tuberculosis who responded to antitubercular therapy began to do so within five weeks. This confirms the findings of previous studies which have indicated that nearly all patients show some improvement after four weeks of therapy.[14,15] Some patients who eventually responded to treatment took longer than five weeks to reach the point at which they could be categorized as showing distinct clinical improvement. Two of these patients, women with scars and small sinuses on the breast, showed minimal activity at baseline. With a paucity of clinical signs to assess, it was difficult to be certain of improvement till late in the course of therapy.

Two patients had tuberculids. This type of cutaneous tuberculosis may have spontaneous remissions and relapses and even appear for the first time after antitubercular therapy is begun.[16] Tuberculids may thus behave differently and not respond to treatment in the manner and time frame as compared to other forms of cutaneous tuberculosis.

Nine patients suspected to have cutaneous tuberculosis did not respond to the therapeutic trial. The reason for the lack of response was incorrect diagnoses in four patients. This validates the concept of the therapeutic test that a lack of response to specific therapy indicates another diagnosis. Other reasons included an inadequate period of treatment in two patients while the diagnosis could not be established in three patients in spite of detailed investigations.

This group of patients with granulomatous diseases with no clues to cause from laboratory investigations, represent a difficult diagnostic problem for which novel strategies need to be developed. Some or all of these three patients may have had drug-resistant tuberculosis but it was not possible to confirm or refute this diagnosis with certainty.

A limitation of this study is the lack of objective criteria to record improvement. While distinct clinical improvement is a simple enough concept to understand intuitively, it is difficult to define in an objective manner. No standard scale is available for measuring the improvement in cutaneous tuberculosis. In our study, the dermatologist examining the patient was not blinded to the duration of therapy at the time he or she evaluated the patient for improvement and this is a possible source of bias.

However, considering the large proportion of patients who showed improvement within five weeks even when examined by the different authors during the study, the effect of such a bias is likely to be small. One strategy to overcome this source of bias would be to photograph lesions at baseline and at follow-up visits and submit the images for evaluation to an investigator blinded to the duration of treatment. It is possible that some patients may have improved earlier than the date they were recorded to show distinct clinical improvement by the examining dermatologist. This early recovery could have been noted by asking the patient to tell us when he / she noticed a change in the lesion. Our choice of end point may have resulted in an overestimate of the period required for recovery but we believe this is more reliable because it is based on objective findings at examination.

In conclusion, this study indicates that the appropriate length of a therapeutic trial in cutaneous tuberculosis is five weeks. With the exception of tuberculids and minimally active disease, this period appears adequate to produce clinically obvious improvement in those who will respond to treatment. A patient who has shown no improvement at all in this time is unlikely to do so with further therapy and the trial of AKT should be terminated. Further, when a patient suspected to have tuberculosis does not respond to standard therapy, it is automatically assumed that he may have drug-resistant disease. This study indicates that other causes need to be considered including a mistaken diagnosis and inadequate therapy or noncompliance before embarking on second line antitubercular drugs.

REFERENCES

1. Kumar B, Rai R, Kaur I, Sahoo B, Muralidhar S, Radotra BD. Childhood cutaneous tuberculosis: A study over 25 years from northern India. Int J Dermatol 2001;40:26-32.
2. Pandhi RK, Bedi TR, Kanwar AJ, Bhutani LK. Cutaneous tuberculosis. A clinical and investigative study. Indian J Dermatol 1977;22:99-107.
3. Ramesh V, Mishra RS, Jain RK. Secondary tuberculosis of skin, Clinical features and problems in laboratory diagnosis. Int J Dermatol 1986;22:578-81.
4. Sehgal VN, Srivastava G, Khurana VK, Shanmark, Bhalla P, Beohar PC. An appraisal of epidemiologic, clinical, bacteriologic and immunological parameters in cutaneous tuberculosis. Int J Dermatol 1987;26:521-6.
5. Sharma RC, Singh R, Bhatia VN. Microbiology of cutaneous tuberculosis. Tubercle 1975;56:324-8.
6. Sehgal VN, Jain MK, Srivastava GP. Changing patterns of cutaneous tuberculosis. A prospective study. Int J Dermatol 1989;28:231-5.
7. Gopinathan R, Pandit D, Joshi J, Jerajani H, Mathur M. Clinical and morphological variants of cutaneous tuberculosis and its relation to *Mycobacterium* species. Indian J Med Microbiol 2001;19:193-6.
8. Margall N, Baselga E, Coll P, Barnadas MA, Moragas JM, de Prats G. Detection of *Mycobacterium tuberculosis* complex DNA by the polymerase chain reaction for rapid diagnosis of cutaneous tuberculosis. Br J Dermatol 1996;135:106-9.
9. Tan SH, Tan HH, Sun YJ, Goh CL. Clinical utility of polymerase chain reaction in the detection of *Mycobacterium tuberculosis* in different types of cutaneous tuberculosis and tuberculids. Ann Acad Med Singapore 2001;30:3-10.
10. Hsiao PF, Tzen CY, Chen HC, Su HY. Polymerase chain reaction based detection of *Mycobacterium tuberculosis* in tissues showing granulomatous inflammation without demonstrable acid-fast bacilli. Int J Dermatol 2003;42:281-6.
11. Arora SK, Kumar B, Sehgal S. Development of a polymerase chain reaction dot-blotting system for detecting cutaneous tuberculosis. Br J Dermatol 2000;142:72-6.
12. Padmavathy L, Rao L, Veliath A. Utility of polymerase chain reaction as a diagnostic tool in cutaneous tuberculosis. Indian J Dermatol Venereol Leprol 2003;69:214-6.
13. Sehgal VN, Sardana K, Sehgal R, Sharma S. The use of anti-tubercular therapy (ATT) as a diagnostic tool in pediatric cutaneous tuberculosis. Int J Dermatol 2005;44:961-3.
14. Ramam M, Mittal R, Ramesh V. How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis. Int J Dermatol 2005;44:121-4.
15. Pandhi D, Reddy BS, Chowdhary S, Khurana N. Cutaneous tuberculosis in Indian children: The importance of screening for involvement of internal organs. J Eur Acad Dermatol Venereol 2004;18:546-51.
16. Thami GP, Kaur S, Kanwar AJ, Mohan H. Lichen scrofulosorum: A rare manifestation of a common disease. Pediatr Dermatol 2002;19:122-6.