

GAMMA GLOBULIN THERAPY IN LEPROSY

A PILOT STUDY^{1, 2}

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Sulfone therapy remains the treatment of choice for leprosy⁽²⁾. Promin was the first sulfone utilized—the year was 1941⁽⁵⁾. Since that time other sulfones, including DDS (diaminodiphenyl sulfone), Diasone (sulfoxone sodium), and Sulphetrone (Solapsone) have been evaluated and have become important drugs for the treatment of leprosy. Unfortunately, the sulfones will not effect satisfactory results in significant numbers of patients, particularly those with lepromatous leprosy. Numerous compounds other than sulfones have been suggested and employed in leprosy. Some have been partially successful, but none has been proven to be equal to or superior in effect to the sulfones⁽³⁾.

Because gamma globulin therapy has been reported to be beneficial as adjunctive therapy in certain chronic bacterial processes^(7, 8, 9, 13, 14), we decided to give this substance to a small group of patients. A review of the literature revealed that gamma globulin had been administered previously to patients with leprosy on a short term basis only, and with equivocal results^(4, 10). The patients treated in the study here reported were selected from a group of patients who presented the most difficult treatment problems at the U. S. Public Health Service Hospital, Carville, La. Each of the five patients selected had not responded to previous therapy. Satisfactory response to any form of treatment during the next several years was not expected in any of the cases.

The dosages of gamma globulin employed varied from 4 to 5 ml. daily intramuscularly. We chose 5 ml. as the maximum dosage primarily because we believed this amount could be tolerated as a single injection on a daily basis for prolonged periods of time^(6, 8). No definite time limits were placed on the treatment schedules, but we anticipated treating each patient with gamma globulin for at least six months. The number of patients to be studied was limited to five because of the inherent difficulties in obtaining the amount of gamma globulin that would be needed for a large scale study.

The case summaries are as follows:

CASE HISTORIES

CASE No. 1. M.B., a 26-year-old white female, developed erythematous lesions over all extremities in 1956, which were thought to have

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resulted from "hypersensitivity" of unknown origin. These resolved following treatment with a corticosteroid, but in 1957 she developed swelling of both ankles and "pericarditis," associated with nasal congestion and nosebleeds. A diagnosis of rheumatic fever was made. Her signs and symptoms were less prominent, with the exception of the nasal congestion, following treatment with bed rest and penicillin. In 1958 erythematous lesions appeared on the back; a year later similar lesions appeared on the face. Again, they responded to corticosteroid therapy. An exacerbation of cutaneous lesions in 1959 led to removal of a specimen of skin for biopsy; histopathologic examination of the biopsy material resulted in a diagnosis of lepromatous leprosy. The patient was admitted to the USPHS Hospital, Carville, La.

Treatment with intravenous Promin was started in July 1959. An exacerbation of the skin lesions occurred within three days, a process characteristic of erythema nodosum. The Promin was discontinued and prednisone therapy started; her condition improved and in October 1959 she was placed on Diasone, one tablet (330 mgm.) twice weekly. Prednisone was continued in a dosage of 30 mgm. daily. Again she developed erythema nodosum, but it was decided to continue the Diasone in low dosages (one tablet weekly). By October 1960 she was tolerating Diasone, three tablets weekly; the prednisone had been gradually reduced in dosage and was discontinued at that time.

Moderately severe erythema nodosum developed in January 1961. The Diasone previously given was replaced by diethylamino diphenyl thiourea (Ciba 1906) in a dosage of 250 mgm. daily, with isoniazid in dosages varying from 100 mgm. to 300 mgm. daily, depending on the ability of the patient to tolerate this medication without troublesome episodes of erythema nodosum. By June 1961 it became apparent that her condition was not improving, recurrent erythema nodosum continued to be a major problem, and many of the lesions had ulcerated.

On September 25, 1961, the patient was placed on *gamma globulin* (in the form of poliomyelitis immune globulin) in a dosage of 4 ml. intramuscularly on a daily basis. The Ciba 1906 was continued in the same dosage (250 mgm. daily). This treatment schedule was continued until March 29, 1962, at which time gamma globulin was discontinued because our supply was exhausted. At the time it was noted that the patient had not had an episode of erythema nodosum following the administration of gamma globulin, except for a mild, brief episode one week after the beginning of the study. She experienced no particular discomfort from the injections, which were given as undivided doses into the upper outer quadrant of the buttocks, sides and sites being alternated each day.

Rather than risk precipitating erythema nodosum with sulfone therapy, we increased the dosage of Ciba 1906 gradually. By June 1962 the patient was receiving this drug in a dosage of 2 gm. daily. On July 23, 1962, isoniazid again was added to the treatment regimen, inasmuch as our past experience with Ciba 1906 in numerous

cases of leprosy indicated that this drug alone was not capable of inactivating the disease. Furthermore, we doubted seriously that the combination of isoniazid and Ciba 1906 in the usual dosages would result in significant improvement; for this reason the isoniazid dosage was increased gradually from 300 mgm. daily on July 23, 1962, to 2,100 mgm. daily (44 mgm./kg.) on October 1, 1962. The latter dosage was continued until April 22, 1963, at which time it was reduced to 600 mgm. daily as a precautionary measure prior to the patient's departure from the hospital on pass. Pyridoxine was administered during this period in a dosage of 50 mgm. twice daily parenterally. At no time did the patient experience side effects suggesting isoniazid toxicity, nor did she have complaints of any type during this period except for a brief, minor episode of erythema nodosum, which occurred four days after the institution of isoniazid therapy.

Although the patient had no complaints, histopathologic examinations continued to show evidence of active lepromatous leprosy. For this reason DDS was started on July 10, 1963, in a dosage of 25 mgm. twice weekly. She continued to take Ciba 1906, 500 mgm. daily, and isoniazid, 600 mgm. daily. On August 26, 1963, the Ciba 1906 was discontinued because this drug was no longer available to us. By September 17, 1963, the dosage of DDS had been increased gradually to 100 mgm. three times weekly. As of December 1, 1963, the patient continued to take DDS and isoniazid without incident. As of December 1964 the patient was discharged with no clinical evidence of leprosy. Only very small numbers of acid-fast bacilli were observed in biopsy material prior to discharge.

Comment.—Our experience with the treatment of leprosy suggests that the dramatic reversal in this patient's ability to tolerate anti-leprosy medication could not have been expected to occur over such a brief period of time, regardless of the method of therapy employed. We have concluded, therefore, that treatment with gamma globulin may have been responsible in some manner for this phenomenon. We emphasize, however, that although the patient remains free from complications, she continues to have cutaneous histopathologic evidence of active lepromatous leprosy. Whether or not the disease will be brought to a stage of inactivity remains questionable.

CASE No. 2. G.R., a 17-year-old white male, was admitted to the U. S. Public Health Service Hospital, Carville, La. in June 1958 with a history of progressive skin eruption over the face, of three years' duration. A year after the onset of the eruption he was diagnosed as having acne. A diagnosis of lepromatous leprosy was made following a skin biopsy taken before admission. An additional point of information obtained in the history was that he had noted the onset of anesthesia in the cutaneous distribution of the radial nerve of the left hand at the age of ten.

At the time of admission examination revealed thinning of the lateral aspect of both eyebrows, edema of the hands, median palsy

on the left, with inability to oppose the thumb and mild bilateral ulnar weakness. Both ulnar nerves were enlarged, but not tender. Glove-type hypesthesia of the upper extremities was present, as was stocking-type hypesthesia of the lower extremities. The facial skin was brownish and somewhat infiltrated. There were superimposed dark red, nodular lesions. Several hyperpigmented macules were present over the trunk; multiple hypopigmented macules were located over the extremities. There were enlarged axillary, inguinal and epitrochlear nodes.

Laboratory work at the time of admission yielded the following data: hemoglobin 13.5 per cent, hematocrit 43 per cent, WBC 4,950 (segmental forms 42, stabs 15, lymphocytes 36, eosinophiles 5, basophiles 2 per cent), FBS 106 mgm. per cent, cephalin flocculation 4+, thymol turbidity 2.7, NPN 24, total protein 7.5 gm. per cent and A/G ratio 3.9/3.4. The lepromin test was negative. Numerous acid-fast bacilli were found on nasal smears and skin scrapings. A skin biopsy revealed changes diagnostic of lepromatous leprosy. X-ray examination of the hands and feet revealed no bony abnormalities. Chest x-ray findings were within normal limits.

Hospital course.—The patient was treated with intravenous Promin without incident until December 1958, when he experienced left ulnar and median neuritis. This episode passed with symptomatic treatment until April 1959, when it recurred. The patient had an opponens transfer in February 1959 for his left median palsy and an anterior transposition and neurolysis of his right ulnar nerve in April 1959.

The patient was started on varying doses of prednisone (15 to 40 mgm. daily) in May 1959 for control of erythema nodosum. The reactive episodes became more frequent and increased in intensity. Temperatures of 105° F orally were not uncommon. In each instance an increase in the corticosteroid dosage was necessary for control, and a decrease in sulfone dosage was also necessary. These reactions occurred once or twice monthly and lasted 10 to 20 days. This continuous chain of reactions with erythema nodosum occurred for two years, with increase in the amount of corticosteroids for control and decrease in the amount of sulfones administered to avoid reactions.

Because of the deteriorating effect of these episodes, Promin was discontinued in July 1959, and Diasone was started in a dosage of one tablet (330 mgm.) daily. The patient was unable to tolerate the latter medication, severe erythema nodosum necessitating its discontinuance a month later. In November 1959 he was placed on Ciba 1906 in a dosage of 0.5 gm. daily. By June 1960 the dosage of Ciba 1906 had been increased to 2 gm. daily. Sulphetrone (0.1 ml. of a 50 per cent solution) intramuscularly was started on a twice-weekly basis in June 1960. It was necessary to stop this medication in September 1960 because of an increase in erythema nodosum activity. In December 1960 all specific antileprosy therapy was stopped because of increasingly severe episodes of erythema nodosum. Treatment with prednisone

and ACTH was continued. Intramuscular Fuadin was also employed in an attempt to ease the situation. Because of the inadvisability of continuing the patient on corticosteroid therapy alone, DDS was added in February 1961, in a dosage of 25 mgm. weekly. The dosage was gradually increased until a level of 300 mgm. weekly was attained. Moderately severe, recurrent episodes of erythema nodosum, associated with high fever, continued, however, and otherwise the patient's condition had not improved since admission.

Inasmuch as an alternative regimen of treatment, that might be expected to benefit the patient, could not be prescribed, he was placed on gamma globulin (poliomyelitis immune globulin) on July 7, 1961. The dosage employed was 5 ml. intramuscularly on a daily basis, administered in the upper outer quadrant of the buttocks. On August 15, 1961, the patient was noted to be free from erythema nodosum. From that date until his discharge on November 18, 1963, he had only one episode of erythema nodosum, and this a mild one. Gamma globulin was discontinued on March 25, 1963, because the supply was exhausted. The patient had received a total of 1,195 ml. The reader is referred to a graph representation of temperatures taken from the patient's medical record (Fig. 1). Elevations of temperature recorded on this graph coincide with episodes of erythema nodosum, except for elevations A and B, which resulted from other causes.

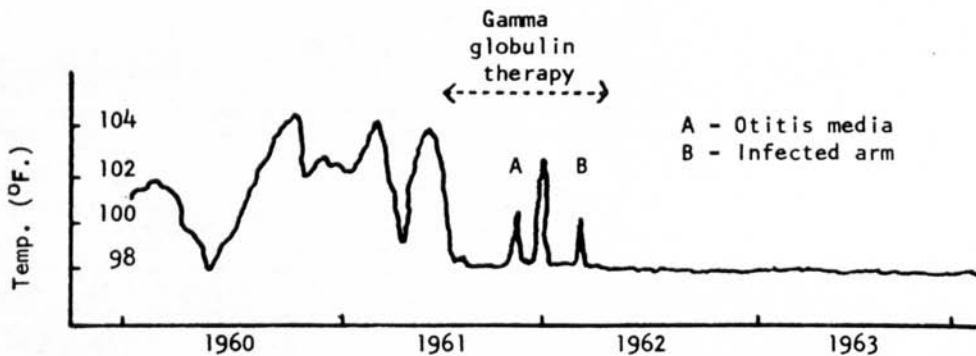


FIG. 1. Case No. 2. Average oral temperatures recorded daily during years 1960 through 1963.

By August 1963 corticosteroid therapy had been withdrawn completely. DDS, which was continued during the period of gamma globulin therapy, was gradually increased; by May 1962 the patient was taking 50 mgm. daily without incident, and by July 1963 he was taking 100 mgm. daily. The latter dosage was continued, without associated problems of any type, until his discharge in November 1963.

Laboratory studies in July 1961 prior to the introduction of gamma globulin therapy in his treatment regimen, revealed a total protein of 6.2 gm. per cent with an A/G ratio of 2.8/3.4. In March 1962 the total protein was 6.3, with an A/G ratio of 4.3/2.0. Serial readings between March 1962 and November 1963 were similar to the latter figures. An incidental finding was that the serum cholesterol ranged from 300 to

355 mgm. per cent prior to gamma globulin therapy; it was 224 mgm. per cent two months after the institution of this therapy and ranged from 146 to 190 mgm. per cent thereafter.

Comment.—This patient's clinical course was such that we doubted seriously that he could have responded similarly to the usual treatment employed in leprosy. Not until after he had been placed on gamma globulin did his condition improve. The change was dramatic and has been maintained. An examination one year following discharge revealed the patient's disease process to be quiescent.

CASE No. 3. E.C., a 36-year-old white female was admitted to the U. S. Public Health Service Hospital, Carville, La., in November 1961. She had developed erythematous lesions of the face and extremities one year prior to admission; a diagnosis of lepromatous leprosy, complicated by erythema nodosum, was made at another institution. Rather than risk exacerbating her condition we did not employ sulfone therapy; she was placed on prednisone, streptomycin, and, later, Ciba 1906. She was admitted to the Carville hospital primarily because of recurrent, severe erythema nodosum. Following admission, streptomycin and prednisone therapy was continued, and isoniazid was added to the regimen. All drugs except prednisone were discontinued in September 1962.

Because her condition had not improved, the patient was started on gamma globulin (poliomyelitis immune globulin), 4 ml. intramuscularly daily, on October 22, 1962. This dosage was continued until December 6, 1962, when it was reduced empirically to 2 ml. daily. This dosage was continued until October 10, 1963, when available supplies of the substance were depleted.

The patient received prednisone in dosages of 10 to 60 mgm. daily from the time of her admission (November 1961), and continued on this medication as of December 1963. During the first three months of gamma globulin therapy she was also treated with Tapazole (30 mgm. daily after starting with low dosages). She became afebrile on October 28 and remained so, and without evidence of erythema nodosum, for two and one-half months. Following this period, however, she again developed recurrent, moderately severe to severe episodes of erythema nodosum associated with fever.

Comment.—This patient, who had been unresponsive to other forms of treatment, was placed on gamma globulin. Following the administration of this substance, she improved considerably. Her condition worsened again, but only after the gamma globulin dosage had been reduced by 50 per cent. On the basis of her clinical response to date, we believe she has not had an overall satisfactory response to gamma globulin.

CASE No. 4. C.L., a 22-year-old white male, was admitted to the U.S. Public Health Service Hospital, Carville, La., in 1939 with a history of erythematous skin lesions for three years. A diagnosis of lepromatous leprosy was made following a skin biopsy made shortly before admission.

The patient remains hospitalized. He has been treated with numerous medications, including chaulmoogra oil, Promin, diphtheria toxoid, Diasone, Ciba 1906, Sulphetrone, isoniazid, and streptomycin. As suggested by the numerous drugs employed, he has not responded favorably to treatment.

On September 28, 1961, the patient was placed on gamma globulin (poliomyelitis immune globulin) in a dosage of 5 ml. intramuscularly daily. Concomitant treatment during this period included ACTH, 20 mgm. twice daily, prednisone, 20 to 30 mgm. daily, streptomycin, 1 gm. twice weekly, and potassium chloride. On March 8, 1962, gamma globulin was stopped. The patient's condition did not improve appreciably either during or following treatment with gamma globulin.

Comment.—This patient had been treated for leprosy since 1939 with unsatisfactory results. A trial on gamma globulin therapy (5 ml. daily, a total of 740 ml.) resulted in no significant change.

CASE No. 5. R.F., a 37-year-old white male, was first admitted to the U. S. Public Health Service Hospital, Carville, La., in 1941, with a diagnosis of lepromatous leprosy. During the following years he was treated with a variety of medications, including chaulmoogra oil, Promin, Diasone, Ciba 1906, Sulphetrone, and Madribon. His overall response was unsatisfactory.

Because of a progressive deterioration in his condition as evidenced by massive lepromatous infiltrations and bleeding into the skin, mucous membranes, and gastrointestinal tract (these bleeding episodes were of undetermined cause), he was placed on gamma globulin (poliomyelitis immune globulin) in a dosage of 4 ml. intramuscularly on October 4, 1961. He was continued on this substance until March 8, 1962, when it was discontinued because of an exhausted supply. Concomitant therapy included prednisone, ACTH, Hydreltrasol, ascorbic acid, Dianabol, Fuadin, and Sulphetrone. There was no evidence of significant improvement. During the latter part of 1962 it became obvious that his condition was terminal. He expired in January 1963. Autopsy revealed far-advanced lepromatous leprosy, arteriolar nephrosclerosis and the aforementioned hemorrhages into the cutaneous structures and gastrointestinal tract. The etiology of the hemorrhagic diathesis remains unknown.

Comment.—This patient, with complicated lepromatous leprosy, received gamma globulin in a dosage of 5 ml. daily, a total of 680 ml. being administered. No improvement in his condition was noted during or following gamma globulin therapy.

DISCUSSION

In our experience, satisfactory results in treatment cannot be achieved in approximately one-third of patients with lepromatous leprosy. In another third some improvement of the patients' condition can be expected, but complete eradication of the disease probably

will not be effected. The remaining third respond quite satisfactorily, if such response achieved over periods of 1 to 10 years can be deemed satisfactory (12). Undoubtedly one reason why patients with leprosy do not respond favorably to treatment is that the sulfones are not sufficiently specific for *Mycobacterium leprae*. Drug resistance, although not proven to be a definite factor, could easily explain many of the failures. The frequent emergence of erythema nodosum (1, 11) as a complicating factor during the course of treatment of lepromatous leprosy is perhaps the most serious limitation to effective utilization of the drugs now available to us. No doubt a high percentage of patients who respond poorly to antileprosy therapy would have a more favorable prognosis were it not for the fact that attempts to administer sulfones are followed by episodes of erythema nodosum, which are frequently severe.

No information was available to us that would suggest what results might be expected from the administration of gamma globulin to cases of leprosy, particularly those complicated by erythema nodosum. Our decision to study the effects of gamma globulin in leprosy was based primarily on a desire to observe its effect, if any, on the overall course of the disease. It was our hope that the administration of this substance would at least alter the situation sufficiently to allow us to proceed with sulfone therapy. The case histories as presented above, of patients No. 1 and No. 2, suggest that such a change may have been effected. Certainly we would not otherwise have expected to achieve similar results.

In none of the patients studied did we observe side effects from the administration of gamma globulin, except for some tenderness at the injection site, which was tolerated easily. This suggests that the substance can be administered in a daily dosage of 5 ml. intramuscularly for periods exceeding one year.

We recognize that two good results out of a total of five patients studied do not provide sufficient information to recommend the administration of gamma globulin as an adjunctive form of therapy for leprosy. We do believe, however, that the results are sufficiently encouraging to warrant further investigation.

SUMMARY

Five patients, each with severely complicated lepromatous leprosy, were treated with gamma globulin in dosages of 2 to 5 ml. intramuscularly on a daily basis for periods ranging from four months to eleven months. In the opinion of the authors, two of the patients responded favorably to treatment, whereas three patients showed no demonstrable benefit. All patients had slight, intermittent tenderness at the injection sites, but there were no demonstrable side effects of significance. The possible future role of gamma globulin in the treatment of complicated leprosy cannot be estimated on the basis of this limited study. The authors believe, however, that additional studies are warranted.

RESUMEN

Cinco pacientes, cada uno con lepra lepromatosa severamente complicada, fueron tratados con gamma globulina en dosis de 2 a 5 ml. intramuscular diariamente, por períodos variables entre cuatro a once meses. En la opinión de los autores, dos de los pacientes respondieron favorablemente al tratamiento, mientras tres pacientes no mostraron beneficios demostrables. Todos los pacientes tuvieron una ligera e intermitente terneza en el sitio de la inyección, pero no hubo efectos colaterales de significación. El posible papel futuro de la gamma globulina en el tratamiento de la lepra complicada, no puede ser estimada sobre la base de este limitado estudio. Los autores creen, sin embargo, que son justificados estudios adicionales.

RÉSUMÉ

Cinq malades, chacun d'entre eux avec une lépre lépromateuse grave et compliquée, ont été traités par des gamma-globulines administrées quotidiennement par voie intramusculaire à des doses de 2 à 5 ml. pendant une durée variant de quatre à onze mois. D'après l'opinion des auteurs, deux des malades ont répondu favorablement au traitement, tandis qu'il n'a pas été possible de démontrer un effet bénéfique chez les trois autres. Tous les malades ont présenté une douleur légère et intermittente à l'endroit d'injection, mais aucune réaction secondaire d'importance n'a été notée. Le rôle futur des gamma-globulines dans le traitement de la lèpre avec complications ne peut être apprécié à la suite de cette étude limitée. Les auteurs croient toutefois que des études supplémentaires sont indiquées.

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