Immunocompetence and transfer factor therapy in uveitis

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SUMMARY A study of the clinical course of 20 patients with uveitis treated with transfer factor is reported. Twelve (60%) of the patients were initially immunoincompetent on screening. Eight of the 12 changed to an immunocompetent status after treatment and could either decrease or discontinue their anti-inflammatory drugs. Five had a statistically significant improvement in visual acuity. One of the 8 initially immunocompetent patients had a statistically significant visual improvement, and 2 decreased or discontinued all drugs, while 3 increased their drugs.

In 1949 Lawrence demonstrated that delayed hypersensitivity to tuberculin can be transferred from sensitive to nonsensitive individuals by injecting leucocytes. It was later shown that a subcellular fraction of lyzed leucocytes can also accomplish passive transfer of delayed hypersensitivity. This fraction was obtained by dialysing the lyzed leucocytes, and therefore consisted of molecules smaller than 10,000 in molecular weight. It was designated as transfer factor. This substance is capable of improving cellular immune responses and has been used clinically in diseases in which demonstrable defects exist in the cellular immunity. Therapeutic benefits have been reported in immunodeficiency diseases, malignancies, and viral illnesses.

In addition to improvement in cellular immunity the possible mechanisms of action may include induction of interferon.

Wolf et al. found that transfer factor therapy was effective in alleviating the mucocutaneous and articular manifestations of Behçet’s syndrome in 4 of 6 patients, while Frenkel et al. found the maintenance oral steroid dosage could be tapered in a patient with severe Behçet’s disease after transfer factor treatment. Kozun et al. found that transfer factor, while mitigating the mucocutaneous lesions and fever of neuro-Behçet’s disease, had no demonstrable effect on the neurological findings. Transfer factor was also found to be effective in herpetic keratoconjunctivitis.

This study was undertaken to assess the effect of transfer factor treatment in uveitis.

Materials and methods
Between January 1975 and June 1978, 20 of the patients with uveitis seen in the eye department of Southwestern Medical School were studied. They were referred because they were not responding to treatment with anti-inflammatory drugs, including local or systemic corticosteroids. In some of the patients corticosteroids were inducing lens changes or glaucoma. The patients were seen at consecutive visits to the eye department, an average of 6 times before transfer factor therapy and 16 times after the start of treatment.

There were 20 patients in the study, 8 were males, 16 were Caucasian, 3 Latin American, and 1 black. The ages ranged from 7 to 74 years with an average of 29.3 years. Sixteen patients had binocular disease and 4 uniocular. The patients were followed up for 2 to 27 months, the average being 18.5 months.

The duration of disease at the time of initiation of the study varied from 1 month to 16 years, the average duration being 5 years.

Informed consent was obtained from the patients. Each patient had a visual acuity assessment with correction and with a pinhole if on mydriatics as indicated. The anterior segment was examined with a slit-lamp, and an anterior chamber count and vitreous cell count was done with the room darkened and with 10 times magnification and a 0.3 mm slit-lamp beam. When the cell count was recorded as a range, the mean value was determined. The average
visual acuity, anterior chamber cell count, and vitreous cell counts before and after transfer factor treatment were recorded (Table 1). Gaps in the table are due to nonavailability of data. All patients were maintained on anti-inflammatory drugs and/or steroids locally, subconjunctivally, or systemically as was required throughout the trial.

The fundus was examined with direct ophthalmoscopy, indirect ophthalmoscopy, Hruby lens, and Goldmann 3-mirror lens. Where indicated fluorescein angiography was done and retinal and internist opinions sought. Investigations were tapered according to the clinical nature of the uveitis. A complete blood count, erythrocyte sedimentation rate, test for lupus cells, and human leucocyte antigen typing were done as indicated. Serology for syphilis and toxoplasmosis, including fluorescent antibody tests, histoplasmosis, coccidiomycosis, and antistreptolysin O titre were also done when indicated. Serum albumin-globulin ratio, serum calcium, purified protein derivative skin tests, antinuclear factor, x-rays of skull, chest, hands, and lumbosacral and sacroiliac joints were tests done when appropriate.

Clinically 9 patients had panuveitis, 4 had anterior uveitis, 2 had posterior uveitis, the remaining 5 having peripheral uveitis, choroidoretinitis, iridocyclitis, retinal oedema and iritis (Table 2). The diagnosis was unknown in 9 cases. The diagnosis was presumed as toxoplasmosis in 2 patients; Vogt-Koyanagi-Harada syndrome, ankylosing spondylitis, sclerosing keratitis in association, syphilis, Reiter's syndrome, and histoplasmosis in 6 others; and probably placoid pigment epitheliopathy, heterochromic cyclitis, and Harada's disease in the remaining 3 patients (Table 2). The patient with Harada's disease had bilateral exudative detachments but no cerebrospinal fluid pleocytosis.
The patients underwent immunological evaluation at Wadley Institute of Molecular Medicine before transfer factor administration, 24 hours after the first dose of transfer factor, and at 3–6-monthly intervals. The immune studies included delayed hypersensitivity skin reactions to mumps, histoplasmin, candida, purified protein derivative, and streptokinase-streptodornase. These tests were read at 24 and 48 hours. The maximum of the 2 reactions was recorded.8

The percentage of E-rosette forming cells (T lymphocytes) was calculated in the peripheral blood as described previously.4 The E-rosette scores were also determined. This method gives semiquantitative information about the E-rosette receptors on lymphocytes. The transformation of lymphocytes in response to phytohaemaggulutinin and pokeweed mitogen was calculated by measuring the incorporation of tritiated thymidine.29

The test for B cell function included the determination of erythrocyte-antibody-complement (EAC) rosette-forming B cells29 and serum immunoglobulin levels. The immunoglobulins were determined by the standard radioimmunodiffusion technique. Lymphocyte transformation response to pokeweed mitogen also represents a B cell function.

The patients were randomised into 2 groups. One group received transfer factor in 5 units/m² once a week for 4 weeks and then every 2 weeks. The interval between injections was increased gradually, in some cases every 3 months if there was clinical improvement. The second group served as a control for the first 4 weeks and received a placebo injection at the same frequency. At the end of the first 4 weeks the code was broken. The patients who were receiving transfer factor were continued on transfer factor and those on placebo were started on transfer factor beginning with weekly injections. As a result of randomisation 5 patients fell into the placebo group and 15 into the transfer factor group.
**Enhanced immune responses with transfer factor therapy**

<table>
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<tr>
<th>Patient</th>
<th>% T cells Pre-treatment</th>
<th>During treatment</th>
<th>T cell score Pre-treatment</th>
<th>During treatment</th>
<th>Phytohaemagglutinin Blastogenic index Pre-treatment</th>
<th>During treatment</th>
<th>Pokeweed mitogen Blastogenic index Pre-treatment</th>
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The transfer factor was prepared from healthy household contacts of the patients, who were between the ages of 18 and 30 years. The donors were tested for their immunological status and also screened for hepatitis B antigen. The donors had to fulfil all the criteria for blood donation. Lymphocytes were collected with the aid of a continuous-flow centrifuge (Cell-trifuge-Aminco). This procedure yielded about 10^9 lymphocytes on the average. One unit of transfer factor was the amount of transfer factor which was obtained from 10^9 lymphocytes. One donation of lymphapheresis, therefore, yielded 100 units of transfer factor. The data were analysed by the Student's t test.

**Results**

Eleven of the 20 patients had an abnormal immune status, while one had a borderline abnormal immune status resulting in 12 (60%) of the patients having defective immunity (Table 2). Tests for B cell function were within normal range except for impaired response to pokeweed mitogen, which is given in Table 3.

Retesting for immunocompetence showed that 8 of 12 patients (67%) showed improvement in immune status after transfer factor treatment. One patient had a borderline response and 3 remained incompetent.

Seven of the immunoincompetent patients had uveitis of unknown aetiology. Two had toxoplasmosis. The remaining 3 had presumed histoplasmosis, plakoid pigment epitheliopathy, and ankylosing spondylitis (Table 2). Out of the 12 immunoincompetent patients 8 improved their visual acuity after receiving transfer factor (2 cases in one eye only), and of these 8 who improved 6 showed an improved immune status (Table 2).

Seven of 20 patients (35%) improved their visual acuity, having less anterior chamber and vitreous cells. Four of these 7 had impaired immunity.

Ten (50%) of the patients in the study improved their visual acuity, and a further 3 improved the visual acuity in only one of their affected eyes. The average age for those improving their visual acuity was 19-7 years, the range being 5-37 years. Five of the 10 patients had uveitis of unknown cause, while the remainder had Harada's disease, posterior multifocal plakoid pigment epitheliopathy, heterochromic cyclitis, and toxoplasmosis, and 1 was associated with sclerosing keratitis.

Six of the patients had a statistically significant improvement in their visual acuity (Table 2). Five of these had abnormal immunity and in 4 of these the cause of the uveitis was unknown.

There was no change in the visual acuity of 3 patients, while 4 patients suffering from syphilis, Reiter's syndrome, ankylosing spondylitis, and uveitis of unknown aetiology had a deterioration of visual acuity. Of these 4 patients who deteriorated 2 had normal immunocompetence, 1 had abnormal immune responses, and 1 had borderline immunocompetence, with change to normal immune responses.
Of the 5 patients who were given placebos initially 4 had better visual acuity and fewer cells after transfer factor treatment than they had before and after the placebo were given (Fig. 1).

Concomitant treatment with the anti-inflammatory drugs, salicylates and indomethacin, and with systemic or subconjunctival steroid could be discontinued completely in 10 patients, namely, patients 1, 4, 6, 8, 9, 12, 13, 16, 17, and 18, and had to be increased in 3 patients, 10, 14, and 19, there being no change in the remaining 7 patients.

Table 3 shows those patients who had abnormality in their T lymphocytes either in the form of a low percentage of T cells (E-rosette forming cells) or diminished lymphocyte transformation in response to phytohaemagglutinin stimulation. Results of lymphocyte transformation in response to pokeweed mitogen, which is a B cell mitogen, are also included in this Table. The normal values for our laboratory are given at the bottom of the Table. If a value was decreased by more than 2 standard deviations, or less than 10 in case of lymphocyte blastogenesis, it was considered as abnormal. The patient numbers correspond to the patient numbers in Table 2.

The patients listed in Table 3 showed improvement in their T cell function. There was also improvement in the pokeweed mitogen blastogenic index. There was no definite relationship between the improvement in the immunological parameter and the significant improvement in uveitis. Six out of the 11 patients who showed statistically significant clinical improvement were those that had showed improvement in the immunological parameters.

Eight of the patients had a normal immune screen. Five of these had panuveitis, 2 had anterior uveitis, and 1 had iridocyclitis. Presumed aetiological diagnoses included Reiter's syndrome, associated sclerosing keratitis, syphilis, Harada's syndrome, probable Harada's syndrome and heterochromic cyclitis, and was unknown in 2 patients. Five of these immunocompetent patients improved their visual acuity, the improvement being statistically significant in 1 patient.

Discussion

It is interesting to note that 12 patients (60%) in this study had impaired immune status in the form of low E-rosette forming T lymphocytes or decreased lymphocyte blastogenesis. Nine of these (75%) showed improvement in the immune responses after transfer factor treatment. The immune responses improved in 8 of these patients to the extent that they were within normal range. Out of the 12 patients with impaired immunity, 7 had uveitis of unknown aetiology. It is possible that certain viruses were aetiological factors in these patients. Transfer factor could be effective through 2 different mechanisms if such is the case. The improvement in cellular immunity would be beneficial in eliminating the viral illness. The transfer factor has also been shown to induce interferon, which is an antiviral substance. Uveitis is also thought to be an autoimmune disease. Suppressor cell dysfunction has been associated with autoimmune problems. Transfer factor may also have a modulating effect on the suppressor helper cells relationship.

Transfer factor has beneficial effects other than improvement in cellular immunity. For example, it is capable of inducing interferon. Clinical benefits in patients with normal immune responses may occur
as a result of interferon induction or other, as yet unknown, effects of this substance.

Certain types of uveitis, such as phacoanaphylactic uveitis and sympathetic uveitis, are thought to be due to the liberation into the circulation of sequestered antigens. It is thought that the antigen antibody reaction initiates the uveitic process and that an anaphylactic process or Arthus-like reaction prolongs the process. It has further been postulated that either a change in the antigen or a modification in the susceptibility of the immunological apparatus to antigens tolerated thus far may be the basis for autoimmune disease.

Eight of the 12 initially deficient patients improved their visual acuity on transfer factor treatment, and 6 of these had also changed to an improved immune status. This clinical correlate suggests that the transfer factor may improve the uveitis by enhancing the patient’s immunity, thus decreasing the actual uveitic process. Possibly suppressor T lymphocytes decrease cytotoxic antibodies and decrease B lymphocyte antibody production.

Ten of the 20 patients who improved their visual acuity in each affected eye had an age range of 5–37 years, the average age being 19-7 years, compared to the series average age of 29-3 years. It appears that the improvement in the uveitis, as monitored by visual acuity changes, occurs in younger patients.

The cellular immunity reaches its peak at about 16 years of age and undergoes a decline after the age of 35. The improvement in younger patients may also have resulted from the fact that they have an immune system more susceptible to enhancement.

Studies of the graphs of the visual acuity response on each patient indicate that the response occurs between 7 and 10 days after the initial injection of transfer factor and the course is then a step-like improvement. In patient 9, in whom transfer factor had been stopped and then resumed, this temporal effect is clearly seen (Fig. 2).

The use of anti-inflammatory drugs and local and systemic corticosteroids could be decreased or discontinued in some cases once transfer factor injection had commenced. In the 10 patients in whom these drugs could be stopped 8 had normal immunity initially. Of the 3 patients requiring increased medication all had normal immunity at the onset.

Patients receiving transfer factor for the Wiskott-Aldrich syndrome have developed autoimmune haemolytic anaemia or lymphomas. A direct relationship between the development of these complications and transfer factor cannot be established, since patients with this syndrome are prone to develop these complications. It has also been sug-

gested recently that patients with B cell defects develop haemolytic anaemia. Increases in immunoglobulin levels have been observed in patients with B cell diseases. One patient also developed hepatitis on transfer factor treatment. Side effects attributable to transfer factor were not observed in our study except for the complaint of pain at the site of the injection. However, in view of the possible suggestion of side effects, one should observe and monitor patients closely if B cell defects exist.

As this pilot study does not have a matched control group and the series is small, no definite conclusion can be arrived at. The clinical correlation between immunoincompetent uveitis, change to immunocompetence with transfer factor treatment, and the improved visual acuity while decreasing anti-inflammatory and steroid drugs treatment suggests it may at present be reasonable for a trial of transfer factor treatment primarily in severe uveitis in immunoincompetent patients when the cause is unknown.

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References

2Lawrence HS. Transfer factor in cellular immunity. In:


Kozin F, Haughton V, Bernhard GC. Neuro-Behcet disease; two cases and neuroradiologic findings. Neurology (Minneapolis) 1977; 27: 1148–52.

