

PREVENTION OF JARISCH-HERXHEIMER REACTIONS BY TREATMENT WITH ANTIBODIES AGAINST TUMOR NECROSIS FACTOR  $\alpha$ 

DANIEL FEKADE, M.D., KYLE KNOX, M.B., KEBEDE HUSSEIN, M.B., AMSEL MELKA, M.B., DAVID G. LALLOO, M.D., RUTH E. COXON, F.I.M.L.S., AND DAVID A. WARRELL, D.M.

**ABSTRACT**

**Background** In patients with louse-borne relapsing fever (*Borrelia recurrentis* infection), antimicrobial treatment is often followed by sudden fever, rigors, and persistent hypotension (Jarisch-Herxheimer reactions) that are associated with increases in plasma concentrations of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-6, and interleukin-8. We attempted to determine whether sheep polyclonal Fab antibody fragments against TNF- $\alpha$  (anti-TNF- $\alpha$  Fab) could suppress the Jarisch-Herxheimer reaction.

**Methods** We conducted a randomized, double-blind, placebo-controlled trial in 49 patients with proven louse-borne relapsing fever. Immediately before the intramuscular injection of penicillin, the patients received an intravenous infusion of either anti-TNF- $\alpha$  Fab or a control solution.

**Results** Ten of the 20 patients given anti-TNF- $\alpha$  Fab had Jarisch-Herxheimer reactions with rigors, as compared with 26 of the 29 control patients ( $P=0.006$ ). The controls had significantly greater mean maximal increases in temperature (1.5 vs. 0.8°C,  $P<0.001$ ), pulse rate (31 vs. 13 per minute,  $P<0.001$ ), and systolic blood pressure (25 vs. 15 mm Hg,  $P<0.003$ ), as well as higher mean peak plasma concentrations of interleukin-6 (50 vs. 17  $\mu\text{g}$  per liter) and interleukin-8 (2000 vs. 205 ng per liter) ( $P<0.001$  for both comparisons). Levels of TNF- $\alpha$  were undetectable after treatment with anti-TNF- $\alpha$  Fab.

**Conclusions** Pretreatment with sheep anti-TNF- $\alpha$  Fab suppresses Jarisch-Herxheimer reactions that occur after penicillin treatment for louse-borne relapsing fever, reduces the associated increases in plasma concentrations of interleukin-6 and interleukin-8, and may be useful in other forms of sepsis. (N Engl J Med 1996;335:311-5.)

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**L**OUSE-BORNE relapsing fever, caused by *Borrelia recurrentis* spirochetes, has been responsible for massive epidemics in North Africa, the Middle East, and Europe during this century. The epidemic at the end of World War II involved some 10 million people.<sup>1</sup> There is a potential for future epidemics wherever war and the movement of refugees or immigrants threaten a breakdown in public health. Since the mortality rate for untreated louse-borne relapsing fever has reached 70 percent in some epidemics,<sup>1</sup> antimicrobial treatment is essential. Although effective in eliminating

spirochetes, this treatment precipitates a potentially life-threatening febrile inflammatory reaction in a majority of patients.<sup>1,2</sup> Fever plus other characteristic symptoms after chemotherapy was first described in secondary syphilis and has become known as the Jarisch-Herxheimer reaction.<sup>3,4</sup> This reaction has been described in a variety of bacterial infections, including brucellosis, leptospirosis, Lyme disease, and relapsing fevers. The clinical and pathophysiologic features of the reaction closely resemble those of a classic endotoxin reaction,<sup>2</sup> but unlike other types of acute sepsis syndrome, the Jarisch-Herxheimer reaction is predictable and less variable in its intensity. One to two hours after treatment with penicillin or tetracycline, patients with louse-borne relapsing fever become restless and apprehensive and intense rigors suddenly develop that last 10 to 30 minutes. The temperature, respiratory and pulse rates, and blood pressure all rise sharply. During the next few hours there is profuse sweating, a fall in blood pressure, and a slow decline in temperature.<sup>1,2</sup> The reaction is distressing to the patient and has a case fatality rate of approximately 5 percent.<sup>1</sup> Just before symptoms of the Jarisch-Herxheimer reaction develop there is a substantial increase in circulating levels of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-6, and interleukin-8.<sup>5</sup>

We have been impressed by the similarities in clinical features and pathophysiologic and cytokine disturbances between the Jarisch-Herxheimer reaction seen in louse-borne relapsing fever and severe sepsis from other causes. The sepsis syndrome, or "systemic inflammatory response syndrome,"<sup>6</sup> has a case fatality rate of up to 60 percent despite treatment with antimicrobial agents and supportive measures. Progression from sepsis to life-threatening shock is initiated by endotoxin released from the cell walls of gram-negative bacteria and by other viral, bacterial, protozoal, and fungal pyrogens or toxins. Studies in animals,<sup>7-9</sup> healthy humans,<sup>10</sup> and patients<sup>11</sup> suggest that TNF- $\alpha$  is the most important mediator in sepsis

From the Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom (K.K., D.G.L., D.A.W.); the Infectious Diseases Unit, Department of Internal Medicine, Black Lion Hospital, Addis Ababa, Ethiopia (D.F., K.H., A.M.); and the Department of Chemical Pathology, Medical College of Saint Bartholomew's Hospital, London (R.E.C.). Address reprint requests to Dr. Warrell at the Centre for Tropical Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom.

but that other cytokines, including interleukin-1 $\beta$ , interleukin-6, and interleukin-8, are also released. Since a variety of microbial components can stimulate macrophages to release cytokines, the systemic inflammatory response syndrome might best be treated by neutralizing the effects of the mediating cytokines with specific antibodies, soluble receptors, or natural receptor antagonists.<sup>12</sup> Animal models may not accurately represent disease processes in humans.<sup>13</sup> Clinical trials in patients with septic shock are difficult to conduct because of the heterogeneity of the patients' ages, infectious agents, and underlying disease and uncertainties about the site of infection. This diversity leads to multiple overlapping subgroups of patients unsuitable for statistical comparison.<sup>14</sup> Since the predictable pathophysiologic and cytokine responses of the Jarisch–Herxheimer reaction resemble models used for the systemic inflammatory response syndrome, we considered that therapeutic interventions similar to those used for the syndrome might be beneficial.

In the present study we investigated the effect of sheep Fab antibody fragments against TNF- $\alpha$  (anti-TNF- $\alpha$  Fab) on the incidence and severity of the Jarisch–Herxheimer reactions resulting from antibiotic treatment of louse-borne relapsing fever. The results may have relevance for the management of both this infection and other types of systemic inflammatory response syndrome.

## METHODS

### Patients

Patients with *B. recurrentis* spirochetes in their peripheral blood film, who had been transferred to the Black Lion Hospital, Addis Ababa, Ethiopia, from other hospitals and health clinics in the city, were recruited for the study if they were between 12 and 60 years old, had no clinical evidence of other diseases, and gave informed consent for hospital admission, treatment, and investigation. The nature of the study was explained to them in their own language (usually Amharic). Those unwilling to join the study were offered the standard treatment (intramuscular penicillin) used throughout Ethiopia. Each patient's clinical history and the results of a physical examination were recorded on standard forms. Patients lay supine in bed throughout the study with intravenous cannulas in both arms.

The sample size of 20 patients given nonspecific sheep Fab antibodies and 20 given anti-TNF- $\alpha$  Fab was based on the results of a previous study in which 82 percent of patients had typical Jarisch–Herxheimer reactions after treatment with penicillin.<sup>5</sup> On the basis of the assumption that specific antibody was 50 percent effective in preventing the Jarisch–Herxheimer reaction, a sample of 40 patients would be sufficient to achieve a power of 80 percent with a type I error of 0.05 in a placebo-controlled trial.

### Antibody

Lyophilized sheep polyclonal anti-TNF- $\alpha$  Fab and nonspecific control Fab were supplied by Therapeutic Antibodies, London. Antibodies raised in sheep by immunization with recombinant human TNF- $\alpha$  in Freund's adjuvant were precipitated with sodium sulfate and cleaved with papain to yield Fab and Fc. The total Fab fraction was isolated and lyophilized. Nonspecific antibodies from an unimmunized donor flock were processed similarly and used as control Fab. For each dose, the contents of four 1.5-g vi-

als of lyophilized anti-TNF- $\alpha$  Fab, each containing approximately 0.25 g of specific anti-TNF- $\alpha$  Fab, were dissolved in 100 ml of 0.9 percent saline. In our patients, this corresponded to a dose of approximately 120 mg of total Fab per kilogram of body weight or 20 mg of specific anti-TNF- $\alpha$  Fab per kilogram. Four vials of control Fab were prepared by the same method, producing solutions indistinguishable in appearance from 0.9 percent saline.

### Treatment

We randomly assigned patients to treatment with anti-TNF- $\alpha$  Fab, control Fab, or 0.9 percent saline alone in a 2:2:1 ratio, strictly in order of their admission to the hospital, using a table of random numbers without a block design. Each patient was assigned a study number referring to a numbered treatment pack that was prepared for administration by a senior laboratory technologist who played no part in the subsequent care or assessment of the patients. The saline group was added to allow assessment of the possible adverse effects of sheep Fab. Once base-line temperature had stabilized (fluctuated by less than 0.5°C within a 30-minute period), the test infusion was given over a period of 30 minutes. On completion of the infusion, 600,000 U of penicillin G procaine was administered by deep intramuscular injection into the anterior thigh and an infusion of 0.9 percent saline was continued at a rate of 1 liter every 8 hours for the next 24 hours.

### Assessment

The Jarisch–Herxheimer reaction was graded as absent (no shivering), mild (shivering), moderate (intermittent rigors), or severe (severe, sustained rigors) by a clinician who was unaware of the patient's treatment. Base-line measurements of rectal temperature, blood pressure, and respiratory and pulse rates were recorded every 15 minutes for 5 hours beginning 1 hour before penicillin treatment; the measurements were then continued at 30-minute intervals for a further 4 hours. Core temperature was monitored with a rectal probe, and blood pressure was measured with an automatic sphygmomanometer.

Blood was withdrawn for spirochete and white-cell counts and cytokine assays 30 minutes before penicillin treatment and 1, 1.5, 2, 4, 8, and 24 hours afterward. White cells were counted in a chamber, and spirochete density was calculated by counting the number of spirochetes per 100 white cells and multiplying the value by the white-cell count. For the cytokine assays 10 ml of blood was collected into endotoxin-free tubes, immediately centrifuged at 100 $\times$ g for five minutes, frozen at -20°C, and transported in dry ice to Saint Bartholomew's Hospital, London, for assays of TNF- $\alpha$  and interleukin-1 $\beta$ , interleukin-6, and interleukin-8 with commercial kits (Medgenix Diagnostics).

### Statistical Analysis

The Mann–Whitney test was used to compare the maximal changes in temperature, systolic blood pressure, and respiratory and pulse rates between groups. The chi-square test with Yates' correction was used to compare the incidence of reactions and the proportion of patients whose blood films were clear of spirochetes at four and eight hours. The two-tailed t-test was used to analyze the differences in peak cytokine concentrations and white-cell counts. The severity of the reactions was compared with use of the Mann–Whitney test corrected for ties (equal values). The control group given saline and the control group given nonspecific Fab were combined for analysis because there was no significant difference between the groups in either physiologic variables or cytokine concentrations.

The study was approved by the research ethics committee of the Faculty of Medicine, Addis Ababa University.

## RESULTS

During the five-week period of the study, August 5 to September 9, 1993, 51 patients were enrolled.

Two were subsequently excluded from the analysis. One had a "spontaneous crisis" while under observation before penicillin treatment. He became feverish, and there was spontaneous clearance of spirochetes from the peripheral blood. The second patient was excluded because no spirochetes could be found in the blood smear taken immediately before penicillin treatment.

The base-line characteristics of the 20 patients treated with specific anti-TNF- $\alpha$  Fab and the 29 controls are shown in Table 1. There were no significant differences between groups.

#### Jarisch-Herxheimer Reactions

The incidence and severity of Jarisch-Herxheimer reactions were lower in the group given anti-TNF- $\alpha$  Fab than in the controls. Thus, 90 percent of those receiving control infusions (26 of 29) had clinically evident reactions, as compared with 50 percent of those receiving anti-TNF- $\alpha$  Fab (10 of 20) ( $P=0.006$  by the chi-square test). In the control group 38 percent had moderate reactions and 10 percent had severe reactions, whereas in the anti-TNF- $\alpha$  Fab group, only mild reactions were observed ( $P=0.004$  by the Mann-Whitney test). The control patients had significantly greater mean maximal increases above base-line values in temperature (1.5 vs. 0.8°C,  $P<0.001$ ), pulse rate (31 vs. 13 per minute,  $P<0.001$ ), and systolic blood pressure (25 vs. 15 mm Hg,  $P=0.003$ ) than the patients treated with anti-TNF- $\alpha$  Fab (Fig. 1). The temperature and pulse rate also fell faster toward normal values in patients given anti-TNF- $\alpha$  Fab (Fig. 1). Maximal changes in respiratory rates were not significantly different between the two groups (mean  $\pm$ SD, 16 $\pm$ 13 breaths per minute in the control group and 9 $\pm$ 14 breaths per minute in the anti-TNF- $\alpha$  Fab group;  $P=0.11$ ).

#### Cytokine Concentrations

In the control group, plasma TNF- $\alpha$ , interleukin-6, and interleukin-8 concentrations increased markedly after treatment with penicillin (Table 2). Levels of TNF- $\alpha$  could not be measured reliably in the patients who received anti-TNF- $\alpha$  Fab; however, these patients had much greater reductions in the peak concentrations of interleukin-6 and interleukin-8. There was no significant difference in the interleukin-1 $\beta$  response between the two groups.

#### Spirochete and White-Cell Counts

The length of time to the disappearance of spirochetes and the extent of the fall in the white-cell count typical of the Jarisch-Herxheimer reaction<sup>1,2</sup> were similar in the two groups. In the control group, the spirochetes were cleared within four hours in 14 percent of patients and within eight hours in 48 percent, as compared with 10 percent and 50 percent,

**TABLE 1.** CHARACTERISTICS OF THE GROUPS BEFORE TREATMENT.\*

CHARACTERISTIC	CONTROL GROUP (N=29)	ANTI-TNF- $\alpha$ FAB GROUP (N=20)
Female sex (no.)	2	1
Age (yr)	24 $\pm$ 6	21 $\pm$ 6
Weight (kg)	51 $\pm$ 6	52 $\pm$ 6
Duration of illness (days)	5 $\pm$ 4	5 $\pm$ 2
Temperature (°C)	39.2 $\pm$ 1.0	39.6 $\pm$ 0.8
Systolic blood pressure (mm Hg)	103 $\pm$ 15	101 $\pm$ 13
Respiratory rate (per min)	32 $\pm$ 8	38 $\pm$ 13
Pulse rate (per min)	105 $\pm$ 18	113 $\pm$ 16
White-cell count (per mm <sup>3</sup> )	3100 $\pm$ 2700	1900 $\pm$ 2300
Spirochete count (per mm <sup>3</sup> )	3300 $\pm$ 3100	3500 $\pm$ 2200

\*Plus-minus values are means  $\pm$ SD. There were no significant differences between the two groups at the 5 percent level by Student's t-test.

respectively, in the group given anti-TNF- $\alpha$  Fab. The white-cell count declined by 3100 $\pm$ 2700 and 1900 $\pm$ 2300 cells per cubic millimeter, respectively, in the control and anti-TNF- $\alpha$  Fab groups.

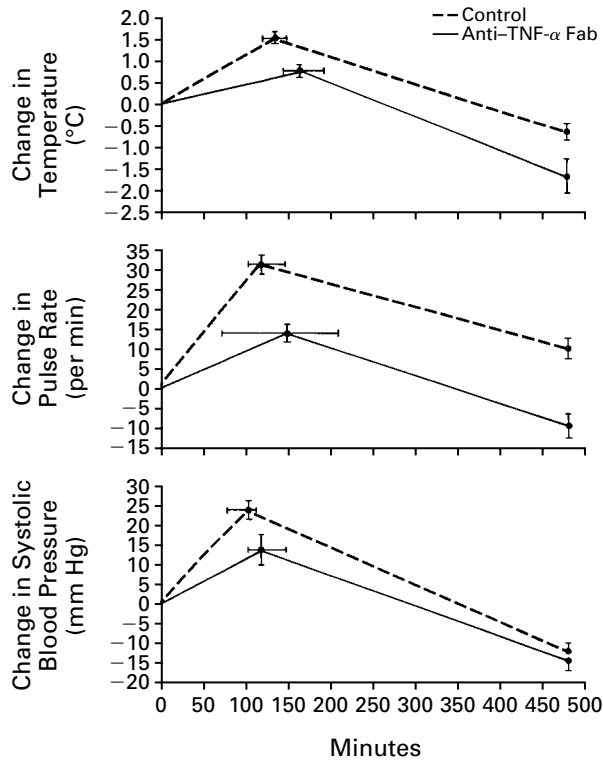
#### Adverse Effects of Fab

One patient who received saline alone died with signs of widespread bronchopneumonia 19 hours after penicillin treatment. Adverse effects occurred in 7 of the 19 patients who received control Fab and in 4 of 20 given anti-TNF- $\alpha$  Fab. There were eight episodes of urticaria, two of dry cough, and one of bronchospasm in the group given control Fab, as compared with three episodes of urticaria and one of vomiting in the group given anti-TNF- $\alpha$  Fab. All these symptoms occurred while the Fab was being infused, and all responded promptly to treatment with either epinephrine (0.5 mg intramuscularly) or chlorpheniramine maleate (10 mg intravenously), or both.

#### DISCUSSION

Murine monoclonal antibodies directed against TNF- $\alpha$  have been reported to increase the mean arterial pressure in terminal septic shock<sup>15</sup> and to produce a dose-related attenuation of fever in cerebral malaria.<sup>16</sup> Recently, human-murine chimeric monoclonal antibodies directed against TNF- $\alpha$  have been shown to cause remissions in patients with other inflammatory conditions, such as Crohn's disease<sup>17</sup> and rheumatoid arthritis.<sup>18</sup> We used sheep polyclonal Fab antibody fragments against TNF- $\alpha$ .

The Jarisch-Herxheimer reaction of louse-borne relapsing fever is an interesting and predictable model of the acute inflammatory response associated with the release of large amounts of TNF- $\alpha$ , interleukin-6, interleukin-8, and other cytokines.<sup>2,5</sup> Ben-



**Figure 1.** Mean ( $\pm$ SE) Maximal Changes in Body Temperature, Pulse Rate, and Systolic Blood Pressure during and after the Jarisch–Herxheimer Reaction in Control Patients and Those Treated with Anti-TNF- $\alpha$  Fab. Time 0 indicates the time before penicillin was given. For the peak values, the medians ( $\pm$ 1 quartile) are also given.

**TABLE 2.** PEAK PLASMA CONCENTRATIONS OF CYTOKINES DURING THE FIRST EIGHT HOURS AFTER PENICILLIN TREATMENT IN PATIENTS WITH LOUSE-BORNE RELAPSING FEVER.\*

CYTOKINE	CONTROL GROUP (N=29)	ANTI-TNF- $\alpha$ FAB GROUP (N=20)	P VALUE
	ng/liter		
TNF- $\alpha$	1764 $\pm$ 1237	10 $\pm$ 6†	<0.001
Interleukin-8	2000 $\pm$ 1925	205 $\pm$ 410	<0.001
Interleukin-6	50 $\pm$ 44	17 $\pm$ 17	<0.001
Interleukin-1 $\beta$	15 $\pm$ 15	9 $\pm$ 11	Not significant

\*Plus-minus values are means  $\pm$ SD.

†The low or undetectable levels of TNF- $\alpha$  in this group were probably explained in part by the masking of epitopes by the therapeutic polyclonal anti-TNF- $\alpha$  Fab.

zylpenicillin attaches to penicillin-binding protein-1 in borrelia spirochetes, producing large surface blebs. The damaged spirochetes are rapidly phagocytosed by circulating polymorphonuclear leukocytes and extravascularly in the spleen.<sup>19</sup> The pyrogen released by borreliae causing relapsing fever has not been identified, but it does not appear to be endotoxin.<sup>19</sup> However, lipoproteins from two other spirochetes, *B. burgdorferi* and *Treponema pallidum*, induce the biosynthesis of tumor necrosis factor in murine macrophages.<sup>20</sup> Corticosteroids and antipyretic agents such as acetaminophen have little or no effect on the life-threatening cardiorespiratory complications of the Jarisch–Herxheimer reaction.<sup>21</sup> Meptazinol, an opioid agonist–antagonist, ameliorated some features of the reaction but did not prevent it.<sup>22</sup>

Treatment with anti-TNF- $\alpha$  Fab significantly reduced the incidence and severity of the Jarisch–Herxheimer reaction. The maximal increases in core temperature, pulse rate, and systolic blood pressure were significantly smaller in patients treated with anti-TNF- $\alpha$  Fab than in patients treated with saline or nonspecific Fab. Treatment with anti-TNF- $\alpha$  Fab profoundly reduced the peak plasma concentrations of interleukin-6 and interleukin-8, probably by blocking the biologic effects of TNF- $\alpha$ . Circulating levels of TNF- $\alpha$  were undetectable in patients who received anti-TNF- $\alpha$  Fab, probably because of the masking of epitopes by the therapeutic polyclonal antibody. It seemed possible that the increases in TNF- $\alpha$  levels during the Jarisch–Herxheimer reaction might have some protective biologic role and that the use of neutralizing antibodies might prevent the successful treatment of louse-borne relapsing fever. However, spirochetes were cleared from the circulation just as quickly in patients treated with anti-TNF- $\alpha$  Fab as in those given nonspecific Fab or saline.

Eleven of the 39 patients given 6 g of control Fab or anti-TNF- $\alpha$  Fab intravenously had mild anaphylactoid reactions. These may have been due to minimal contamination with Fc fragments or chymopain, which are known to cause reactions.<sup>23</sup> In the future, chymopain and its related enzyme will be coupled to a solid-phase support so that they can be extracted, and residual Fc fragments will be eliminated on an ion-exchange column or by prolonged digestion with papain. Another sheep polyclonal antibody (Digibind, Wellcome) has proved to be safe during many years of clinical use for digitalis-induced toxicity.

Further studies have been planned in which Fab purified by affinity chromatography will be used in an attempt to eliminate side effects and to allow measurement of the dose response. There is some evidence from studies in animals that mixtures of antibodies neutralizing various mediators involved in the systemic inflammatory response syndrome may be more beneficial than the use of antibodies against

a single initiator or mediator.<sup>24</sup> Because of their synergistic effects, a combination of antibodies directed against TNF- $\alpha$  and interleukin-1 $\beta$  or other cytokines may be optimal in the prevention of the Jarisch-Herxheimer reaction and perhaps in other systemic inflammatory response syndromes.<sup>25,26</sup>

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