UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

CONSENT TO BE A RESEARCH SUBJECT

A RANDOMIZED STUDY TO EVALUATE

DAPSONE PLUS TRIMETHOPRIM VERSUS TRIMETHOPRIM-SULFAMETHOXAZOLE

FOR TREATMENT OF PNEUMOCYSTIS PNEUMONIA (PCP) IN AIDS

I. Introduction

Pneumocystis carinii pneumonia (PCP) is a very common lung infection in people who have AIDS. Two medications have been used to treat this infection: pentamidine and trimethoprim-sulfamethoxazole (TMP-SMX) (trade name Septra® or Bactrim®). TMP-SMX is the standard first treatment. It is usually given intravenously but many patients have been treated orally with good results. Both treatments have high frequency (55%) of serious side effects which may be very severe or even life-threatening, requiring discontinuation of therapy. Treatment requires several weeks and the infection may occur again, so it is important to identify additional medications which can be used to treat pneumocystis. It is also important to find good oral therapies that can be used to treat pneumocystis. An oral medication called dapsone combined with trimethoprim is as effective for treatment of pneumocystis in rats as TMP-SMX. Recently at San Francisco General Hospital a preliminary study was done using dapsone and trimethoprim (DS/TMP) as the treatment for PCP in AIDS patients. The results were very encouraging; it was as effective as intravenous TMP-SMX and the rate and severity of side effects was low. This study is designed to compare oral dapsone plus TMP and oral TMP-SMX with respect to effectiveness and side effects.

II. Study Design

The diagnosis of pneumocystis will be established by looking at a sample of sputum or material from the lung obtained by bronchoscopy. Patients having PCP will be randomly assigned to receive either dapsone/TMP or TMP-SMX, but neither the subject or investigator will know which drug is being given. All pills will look alike and everyone will take the same number of pills, some of which will be placebo (i.e., the pill base without the medication) so that it will not be possible to tell which drug is used for treatment. A doctor of pharmacy will know which medication is administered and will keep careful control. All patients will take trimethoprim four times a day. In addition, I will take 1) dapsone or placebo once a day plus 2) placebo or sulphamethoxazole four times a day. The duration of the therapy will be 3 weeks. Treatment for the first 2 weeks will be given in the hospital. The last week will be supervised in the outpatient clinic if discharge is clinically indicated. A history, physical, and various laboratory examinations will be done on a regular basis and if there is no response to therapy evaluated by x-ray and examination, or if severe toxicity develops, a switch will be made to pentamidine isethionate, which is a standard therapy for pneumocystis with proven efficacy.

III. General Procedures

The general medical care, x-rays, blood tests, and breathing tests will be the same as those used standardly in patients undergoing treatment for pneumocystis pneumonia. (A list of specific tests and procedures and frequency is attached to this consent form.)

Certain studies will be done which might not be a routine part of therapy. These include a bronchoscopy evaluation at the end of therapy if bronchoscopy was done to establish the diagnosis, and blood tests to measure the amount of dapsone and TMP-SMX in the bloodstream on certain days after a dose of medication. I will also have urine collected to see how much of the drugs are excreted in the urine.

I will be monitored very closely and if severe toxicity develops which might be a result of the drug therapy, I will be switched to pentamidine isethionate. If my physicians feel that I have failed to respond clinically to therapy, I will also be evaluated for a switch to pentamidine isethionate.

IV. Risks

Dapsone has been used to treat other medical conditions in a large number of patients. Various toxicities have been identified including suppression of the bone marrow, which means affecting the ability of the parts of the body which form red blood cells, white blood cells and platelets, to function properly. Dapsone may also cause rashes of various kinds, some of which may be severe or even life-threatening. Dapsone has been used in patients with AIDS who have had PCP. It has the same kinds of toxicity that have been seen in other patient populations given dapsone, including skin rashes and lowered blood counts.

TMP-SMX has been used in AIDS patients as one of the mainstays of therapy for PCP. It has been associated with side effects including rash, bone marrow toxicity resulting in anemia and lowered blood counts of white cells and platelets. It is usually given by vein. Oral therapy has been widely used elsewhere but is not the standard at San Francisco General Hospital; oral TMP-SMX or dapsone-TMP may prove to be less effective than standard treatment or have more side effects.

Side effects of either therapy are reversible with discontinuation of the drug in those situations in which toxicity is identified early. If a severe reaction is identified, the drug will be discontinued and pentamidine substituted. There may be additional unanticipated toxicities such as liver or kidney problems, and these will be monitored very closely. I may be randomized to receive the form of therapy which ultimately proves to be the less effective or more toxic of the two.

If I am injured as a result of being in this study, treatment will be available. The cost of such treatment may be covered by the University of California, depending upon a number of factors. The University does not normally provide any other form of compensation for injury. For information on this I may call 415-476-1814.

If I participate in this study, I will be charged only for the routine laboratory tests, clinic visits, and hospitalization that would be part of my standard care if I were not on study. The special studies described in section III above will be free of charge to me.

V. Benefit

Dapsone plus trimethoprim may prove to be a more effective therapy and/or have a lower rate of side effects than TMP-SMX. I may receive the form of therapy which ultimately proves to be the more effective therapy. Both forms of therapy will be administered orally, therefore no intravenous or intramuscular injections will be administered unless it becomes necessary because of another problem during my hospital course.

VI. Alternatives

The alternative to participating in this study is standard therapy with TMP-SMX, usually administered intravenously, or pentamidine intravenously. Both forms of therapy are associated with frequent (>50%) side effects.

VII. Questions

I have had the opportunity to talk with Dr. Constance Wofsy or Dr. Ileana Medina or their designee _____. If I have any questions about the study I may call Dr. Wofsy or Dr. Medina at 821-8830.

VIII. Confidentiality

Records will be kept as confidential as possible under the law. Records as related to this study may be made available to designated University research associates and the Food and Drug Administration according to Federal regulations and, under certain circumstances, my name may be revealed.

IX. Consent

My participation is this study is entirely voluntary. I may refuse to enter the study or withdraw at any time. If I do so, this will in no way interfere with my medical therapy. I will be given a copy of this consent form and a copy of the Experimental Subject's Bill of Rights.

_____ _____

Signature of Volunteer Date

_____ _____

Signature of Investigator Date

_____ _____

Signature of Witness Date

3/3/86

DAPSONE/TMP VS TMP-SMX PCP STUDY LABWORK SCHEDULE

TREATMENT	
Baseline	CBC, Retics, plates, ESR, SMA-20, LDH, CXR, U/A, skin tests, ABG, PFT, Ga scan, Hepatic serology, G6PD, EBV and CMV titers, VDRL, Met Hgb level *
Day 1	CBC, plates
Day 3	CBC, Retic, plates, SMA-20, LDH, CXR, Dapsone and sulfamethoxazole levels *
Day 6	CBC, Retics, plates, SMA-20, LDH
Day 7	U/A, CXR, Dapsone level, Met Hgb level *
Day 9	CBC, Retics, plates, SMA-20, LDH
Day 12	CBC, Retic, plates, SMA-20, LDH
Day 14	U/A, CXR, Dapsone level, Met Hgb level *
Day 15	CBC, Retics, plates, SMA-20, LDH
Day 18	CBC, Retics, plates, SMA-20, LDH
Day 21	CBC, Retics, plates, SMA-20, LDH, ESR, CXR, ABG, PFT, Ga lung scan, Dapsone level, Met Hgb level, repeat diagnostic procedure to check for Pneumocystis clearing. *

END OF THERAPY	If therapy is stopped before day 21, note event and draw same labs as for day 21.
CHANGE IN THERAPY	If therapy is changed, state why and what new regimen and draw: CBC, plates, SMA-20, CXR, ABG.

FOLLOW-UP POST TREATMENT	
Day 6-8	CBC, diff, platelets, ESR, SMA-20, CXR
1 month	CBC, diff, platelets, ESR, SMA-20, CXR
3 months	CBC, diff, platelets, ESR, SMA-20, CXR
6 months	CBC, diff, platelets, ESR, SMA-20, CXR
9 months	CBC, diff, platelets, ESR, SMA-20, CXR

PLEASE SEE KEY ON NEXT PAGE FOR DEFINITIONS

* = Not routine part of patient care for PCP

KEY TO STUDY LABWORK SCHEDULE

CBC = Complete blood count

Retics = Reticulocytes

Plates = Platelets

ESR = Sedimentation rate

SMA-20 = Blood chemistry and electrolytes

LDH = Liver function test

CXR = Chest x-ray

U/A = Urinalysis

ABG = Arterial blood gases

PFT = Pulmonary function tests

Ga scan = Gallium scan

* G6PD = Glucose 6 phosphate dehydroginase

EBV = Epstein-Barr virus

CMV = Cytomegalovirus

VDRL = Syphilis test

* Met Hgb = Met hemoglobin level

* = Not routine part of patient care for PCP

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EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1) To be told what the study is trying to find out,

2) To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice,

3) To be told about the frequent and/or important risks, side effects or discomforts of the things that will happen to me for research purposes,

4) To be told if I can expect any benefit from participating and, if so, what the benefit might be,

5) To be told the other choices I have and how they may be better or worse than being in the study,

6) To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study,

7) To be told what sort of medical treatment is available if any complications arise,

8) To refuse to participate at all or to change may mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study.

9) To receive a copy of the signed and dated consent form,

10) To be free of pressure when considering whether I wish to agree to be in the study.

If I have other questions I should ask the researcher or the research assistant. In addition, I may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. I may reach the committee office by calling: (415) 666-1814 from 8:00 AM to 5:00 PM, Monday to Friday, or by writing to the Committee on Human Research, University of California, San Francisco, CA 94143.

Call X1814 for information on translations.

12/1/78