

METHOD OF TREATMENT OF RHEUMATOID ARTHRITIS

REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of my earlier application having the Ser. No. 926,688, filed July 21, 1978, said earlier application being incorporated herein as if fully presented and of divisional application Ser. No. 972,634 filed on Dec. 22, 1978, both are abandoned.

BACKGROUND OF THE INVENTION

Rheumatoid arthritis, commonly referred to as RA, is the second most crippling disease in man, ranking immediately behind cardiovascular defects. Until recently no effective treatment for RA has been known. A number of drugs which are moderately effective in the treatment of this disease have been found, examples being D-penicillamine which is β,β -dimethylcysteine and certain compounds of gold, such as gold sodium thiomalate, aurothioglucose and sources of auric or aurous ion.

Of these compounds, the most promising is the recently discovered penicillamine, a natural metabolite of penicillin. Unfortunately, not all patients respond to this medication; also, it carries with it considerable toxicity so that it can, in fact, be lethal. Another difficulty is that penicillamine is slow-acting so that generally it requires 8 to 12 weeks before it can be determined whether the patient is responding and whether the dosage needs adjusting. D-penicillamine usually produces a decrease in the titer of rheumatoid factor, an index of its specific therapeutic efficacy for this human disease. There are no genuine animal models of rheumatoid arthritis.

At the present time, most rheumatologists treat moderately severe RA that has not responded to salicylates with either a gold compound or D-penicillamine. Penicillamine is also used initially in some patients with severe RA, and those in whom rheumatoid lung disease, vasculitis, amyloidosis, Felty's syndrome or rheumatoid nodulosis complicate the clinical picture.

Publications on the use of D-penicillamine make it clear that the dosage employed in the past for treatment of RA has frequently been too high; it is now generally agreed that a dosage of 1.5 g/day is the maximum required. It still has not been determined how long D-penicillamine therapy in RA should be continued, some rheumatologists taking the position that the drug should be continued indefinitely if it is well tolerated while others attempt to reduce the daily maintenance dose gradually in order to determine the minimum quantity of drug necessary for sustaining remission of the disease.

As is clear from the above, D-penicillamine, while for some RA patients the drug of choice at the present time, presents major difficulties, both with respect to toxicity and to the method of use. It is also frustrating that the mechanism by which the compound acts therapeutically is not understood, this lack of understanding having made it difficult to use this compound as a base from which to explore in the search for compounds having a higher therapeutic efficacy, this efficacy being defined as the ratio of the dose causing toxicosis to that required for therapeutic effectiveness. One clue is at hand, namely, that the efficacy of the compound D-penicillamine is linked to the presence of a sulfhydryl group in the molecule. The naturally occurring amino acid cysteine itself also has a sulfhydryl group in the molecule but

is ineffective in the treatment of RA, because it dimerizes to form cystine *in vivo*, and is metabolized by amino acid oxidases and cysteine desulfhydrase to a much greater degree than penicillamine. The dimer, cystine, excreted in the urine in excessive amounts in a hereditary disorder, cystinuria, forms kidney stones in quantity such that they may be lethal, since the dimer is relatively insoluble while cysteine itself is quite soluble. Further, it is evident that the equilibrium between the monomer and the dimer is far over on the side of the dimer, since, otherwise, in patients with cystinuria, dissociation of cystine to the soluble monomer would prevent the formation of cystine stones. D-penicillamine proved to be effective in the treatment of cystinuria because the asymmetrical dimer that is formed—a combination of one molecule of cysteine and one molecule of D-penicillamine—possesses a relatively high solubility so that it is readily excreted from the body.

While D-penicillamine has been more widely used than either the L-isomer or the racemic mixture, it is recognized that any of the three forms may have unique value in specific instances, so that the term "penicillamine" as used herein will be taken to include both isomers and the racemic mixture.

As aforementioned, the mechanism by which penicillamine causes remission of RA is unknown. Just as unknown is the cause of RA itself. However, one reason why penicillamine was investigated was the fact that penicillin which is generally well tolerated by the body, is metabolized in part to penicillamine so that it is apparent that the body can tolerate penicillamine also even if in smaller quantity. I have found that certain closely related compounds which are not natural metabolites of penicillin are at least as effective as penicillamine for the treatment of RA as well as of cystinuria and heavy-metal poisoning.

SUMMARY OF THE INVENTION

Cysteine derivatives useful in the treatment of RA and having lower toxicity and greater therapeutic effect than penicillamine are alpha-substituted cysteines, beta-monosubstituted cysteines, beta-disubstituted cysteines other than penicillamine, alpha-substituted cysteines which are either mono- or di-substituted in the beta position, and N-acetyl derivatives of each of the above which are hereinafter more fully set forth.

The specific sulfhydryl compounds useful in the treatment in RA are members of the following 5 groups:

1. Cysteine derivatives in which one of the beta hydrogens is replaced by Cl, CH₃, C₂H₅, CH₂OH or CH₂CH₂OH;

2. Cysteine derivatives in which both of the beta hydrogens are replaced by one of the following pairs of substituents:

chloro,	chloro,
methyl,	chloro,
ethyl,	chloro,
methyl,	ethyl,
ethyl,	ethyl,
hydroxymethyl,	hydroxymethyl,
hydroxyethyl,	hydroxyethyl,
hydroxymethyl,	hydroxyethyl,
methyl,	hydroxymethyl,
methyl,	hydroxyethyl,
ethyl,	hydroxymethyl,
ethyl,	hydroxyethyl,
chloro,	hydroxymethyl, and