

[54] **TREATMENT OF ARTHRITIS WITH
MYCOPHENOLIC ACID AND DERIVATIVES**

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[21] Appl. No.: **360,292**

[52] **U.S. Cl.**..... **424/180; 260/210; 260/343.2 R**

[51] **Int. Cl.**²..... **A01N 9/00**

[58] **Field of Search**..... **424/180; 260/210, 343.2 R**

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Smith**

[57] **ABSTRACT**

Mycophenolic acid or its glucuronide is administered to patients suffering from inflammatory arthritis for the alleviation of their arthritic symptoms.

4 Claims, No Drawings

TREATMENT OF ARTHRITIS WITH MYCOPHENOLIC ACID AND DERIVATIVES

BACKGROUND OF THE INVENTION

Inflammatory arthritis is a fairly common problem usually attacking the older segment of the population although extremely severe cases of inflammatory arthritis are found, through infrequently, in younger persons.

Inflammatory arthritis may be classified into two groups based on the presence or absence of a serum rheumatoid factor. The sero-positive group includes rheumatoid arthritis and arthritis associated with connective tissue or collagen disease including systemic lupus erythematosus and polyarteritis (periarteritis nodosa). The sero-negative group includes psoriatic arthritis, ankylosing spondylitis and arthritis associated with ulcerative colitis, regional ileitis and Whipple's disease. Other forms of arthritis such as degenerative

joint disease (osteoarthritis) and arthritis caused by metabolic or endocrine disorders, are also sero-negative but are not classified with inflammatory arthritis. [For a discussion and classification of arthritis, see for example Harrison's Principles of Internal Medicine, Ed. Wintrobe et al., 6th Edition (McGraw-Hill Book Co., New, N.Y. 1970) Section 13, particularly pages 140 -1].

Inflammatory arthritis, generally, and rheumatoid and psoriatic arthritis in particular have been subject to more or less successful drug therapy for a number of years, the most acceptable of the drug treatments being either gold therapy or the use of the anti-inflammatory drugs - aspirin, indomethacin and butazolidine. Neither of these treatment methods are free from defects. Gold therapy and aspirin administration are not uniformly successful and the two more recently introduced anti-inflammatory drugs, indomethacin and butazolidine, are frequently toxic at therapeutic levels, usually necessitating a dose reduction, if not outright withdrawal, of the drug followed by a return of the arthritic symptoms. Other drug therapy of arthritis, such as the hormonal approach employing corticoids, has fallen into relative disuse, either for failure to alleviate the symptoms to the degree thought desirable or because of the extreme severity of the side effects accompanying their administration.

Mycophenolic acid is produced by various strains of fungi of the *Penicillium brevicompactum*, *Penicillium stoloniferum* and *Penicillium urticae* groups. The compound was the first biologically-active compound isolated from a mold. The initial isolation was carried out by Gosio in 1896 (Gosio, Rivista d' Igiene e Sanita' pubblica, Ann., 7 825, 869, 961 [1896]). Structure work was effected largely through the efforts of Raistrick et al. from 1932 to 1935 (Raistrick et al., Biochem. J. 26, 1441 [1932]; Biochem J. 27, 654 [1933]).

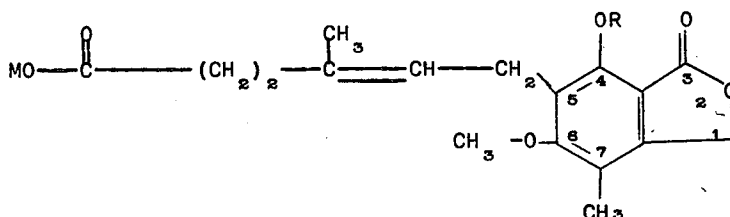
Mycophenolic acid is known to exhibit antifungal, antiviral and antibacterial activity. [See for example, J. Gen. Virol. 4, 629 (1969); J. Antibiotics 22, 297 (1969).]

Mycophenolic acid β -D-glucuronide is described by Ando et al. in J. Antibiotics, 23, 408 (1970) and its anti-tumor activity is set forth in that same article.

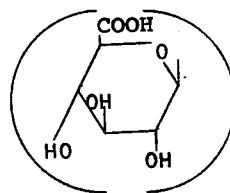
It is an object of this invention to provide a new drug for the treatment of arthritis and for the alleviation of arthritic symptoms which is devoid of certain of the deficiencies of other drugs employed in the past for these purposes.

SUMMARY OF THE INVENTION

In fulfillment of the above and other objects, this invention provides a method of treating inflammatory arthritis comprising administering to a human suffering therefrom an arthritic symptom relieving amount of a compound of the formula



wherein M is hydrogen, potassium, sodium or ammonium and R is hydrogen or β -D-glucuronidyl



When M is hydrogen and R is hydrogen, the above compound is named systematically as 6-[4-hydroxy-7-methyl-6-methoxy-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid or mycophenolic acid. When R is β -D-glucuronidyl and M is hydrogen, the resulting compound is mycophenolic acid β -D-glucuronide or, systematically, 6-[4-(β -D-glucopyranosylglucuronate)-4-methyl-6-methoxy-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid. Other non-toxic salts than those listed above can also be employed.

Mycophenolic acid, mycophenolic acid β -D-glucuronide or salts thereof are administered by the oral route to a human suffering from inflammatory arthritis, such as rheumatoid or psoriatic arthritis. For oral use, mycophenolic acid, its β -D-glucuronide, or salts thereof are administered in the form of tablets or capsules or as a liquid solution or suspension. A preferred mode for oral administration is via telescoping gelatin capsules. A typical useful formulation employing capsules is prepared as follows:

9.4 kg. of mycophenolic acid isolated from a fermentation medium is thoroughly mixed with 4.7 kg. of starch and the mixture loaded into empty telescoping

gelatin capsules. Each capsule contains the following ingredients

400 mg. mycophenolic acid
200 mg. starch

In the above formulation, mycophenolic acid β -D-glucuronide, prepared by the method of Ando et al. (supra) can be substituted for mycophenolic acid.

In the above formulation it has been stated that it is preferred to employ the drug in the form of the free acid; however, the sodium, potassium or ammonium salts are also effective. Formulations employed for the salts are substantially the same as those indicated above for the free acid.

In carrying out my novel treatment method, patients diagnosed as suffering from inflammatory arthritis are treated with from 2 to 5 g. of mycophenolic acid or an equivalent amount of its glucuronide or of a salt thereof per day. The daily dosage should be divided into either 2 or 3 doses.

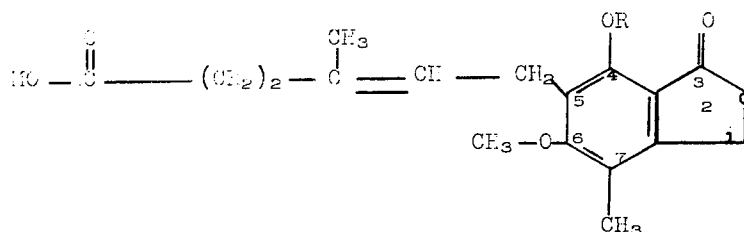
An example of the use of the treatment method of this invention is as follows: A male subject 22 years old who had been diagnosed as suffering from psoriatic ar-

A second, female patient of 46 years was diagnosed as suffering from psoriatic arthritis with hips, left wrist, and sacroiliac involved. She was given from 800 to 1600 mg of mycophenolic acid every eight hours for a 12-week period. Subjective improvement was noticed at the end of one week with the following comments: There was less pain in wrist and hips, less swelling of wrists (an objective improvement) and increased range of rotation. Again, in this instance, the need for aspirin was eliminated.

Mycophenolic acid β -glucuronide as well as cationic salts of mycophenolic acid can be employed in the treatment of inflammatory arthritis at dose levels equivalent to those specified above for mycophenolic acid itself. By equivalent dose levels is meant the same weight of mycophenolic acid per dose.

I claim:

1. The process of treating inflammatory arthritis in humans which comprises administering by the oral route to a human suffering therefrom an arthritis symptom relieving amount of mycophenolic acid or a derivative thereof represented by the following formula



thritus two years previously was found to have the following joints involved in his arthritis: shoulders, hips, right wrist, right hand, proximal interphalangeal joints of third and fourth fingers and distal interphalangeal joint of the thumb. The rheumatoid factor was negative indicating that the disease involved was psoriatic arthritis. Mycophenolic acid was administered to the patient at the rate of 1200 to 2400 mg every 12 hours over a 6 week period. Improvement was noticed at the end of 3 weeks as follows: The patient mentioned that there was improved comfort, decreased morning stiffness and he no longer needed to take aspirin.

wherein M is hydrogen, potassium, sodium or ammonium and R is hydrogen [or β -D-glucuronidyl].

2. A process according to claim 1 in which the arthritis treated is rheumatoid arthritis.

3. A process according to claim 1 in which the arthritis treated is psoriatic arthritis.

4. A process according to claim 1 in which from 2-5 g. per day of drug is administered to the arthritic patient.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,880,995

DATED : April 29, 1975

INVENTOR(S) : E. Linn Jones

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, line 8, "through" should read --though--.

Column 4, line 36, delete "[or β -D-glucuronidyl]".

Signed and Sealed this

eighth Day of June 1976

[SEAL]

Attest:

RUTH C. MASON

Attesting Officer

C. MARSHALL DANN

Commissioner of Patents and Trademarks