A New Medical Approach to the Treatment of Osteoarthritis

Report of an Open Phase IV Study with Ademetionine* (Gumbaral)†

RAINER BERGER, M.D.
HORST NOWAK, Ph.D.
Frankfurt am Main, Federal Republic of Germany

A non-controlled clinical phase IV trial was carried out involving 20,641 patients with osteoarthritis of the knee, the hip, and the spine and also with osteoarthritic polyarthritis of the fingers, who were treated with ademetionine tablets given in a fixed dosage schedule for eight weeks. No additional analgesic/antirheumatic treatment was allowed. Nevertheless, concomitant medication for other diseases was permissible. The efficacy was described as "very good" or "good" in 71 percent of cases, as "moderate" in 21 percent, and as "poor" in 9 percent of cases. The tolerance was assessed as very good or good in 87 percent, as moderate in 8 percent, and as poor in 5 percent of cases. The trial therapy was discontinued prematurely because of symptoms of intolerance in 5 percent of the patients and because of a lack of efficacy in 2.3 percent of cases.

Since its discovery by Cantoni [1] in 1952, ademetionine (SAMe) has been investigated with respect to its biochemical actions in animals and humans, and as a so-called active methyl compound it has sometimes been compared with ATP [2].

In addition to its involvement in approximately 40 biochemical reactions (transmethylation, transsulfuration, and transaminopropylation), pharmacodynamic actions with an influence on pain and inflammation have been demonstrated in animal experiments [3] and unequivocal effects have been shown on the dopaminergic system [4] (Dimpfel W, personal communication).

On the basis of various investigations, there is also evidence to suggest a peripheral analgesic and anti-inflammatory effect of the direct products of conversion and metabolism of putrescine, spermine, and spermidine [5–7]. In vitro investigations carried out on human chondrocytes and reported in this supplement by Harmand et al suggest that ademetionine has a positive influence on cartilage metabolism.

Although efficacy and tolerability were adequately documented for the indication of active inflammatory osteoarthritis at the time of registration by the German health authorities, and oral administration is considered to be completely innocuous from a toxicologic point of view, it seemed advisable to meet the worldwide demand for further information about drug safety through a broadly devised phase IV trial.

PATIENTS AND METHODS

The trial was carried out by orthopedic surgeons, physicians, and general practitioners, each of whom enrolled five patients in their general practices. Patients over 40 years of age with painful osteoarthritis of the knee, hip, and/or spine were admitted to the trial. Patients with painful osteoarthritic polyarthritis of the fingers (Heberden/Bouchard) were also admitted. The duration of

Requests for reprints should be addressed to Dr. med. Rainer Berger, Degussa Pharma Gruppe, Daimlerstrasse, 25, D-6000 Frankfurt am Main 1, Federal Republic of Germany.

*Ademetionine is a synonym for S-adenosylmethionine.

†The work presented herein was based on the administration of Gumbaral tablets, registered trademark of Homburg Degussa Pharma Gruppe, Frankfurt am Main, Federal Republic of Germany, kindly supplied by BioResearch, Milan, Italy.

the disease was to have been at least one year. Although there is no known contraindication for ademetionine, as a precaution, patients with florid duodenal/gastric ulcer, with hematologic diseases, or with severe renal insufficiency were excluded. Another criterion of exclusion was immunosuppressive treatment or the intra-articular administration of corticosteroids, carried out up to three months before the start of the study.

No additional analgesic, anti-inflammatory, or other antirheumatic treatment was allowed. In the case of patients who had previously been receiving such treatment, it had to be indicated whether this had been given up to just before the start of the trial medication. Similarly, no concomitant antidepressive medications were allowed either. The nature, frequency, and duration of any additional physical therapy were to be documented.

The trial medication was to consist of three doses of two tablets in the first week, two doses of two tablets in the second week, and two doses of one tablet from the third week on; each tablet of ademetionine consisted of 200 mg. Within this trial, medication was given for eight consecutive weeks.

RESULTS

Patient Data. Finally, 20,641 trial forms were received. Female patients predominated (58 percent). As expected, the age distribution shows that the majority of patients (roughly 80 percent) were at least 50 years old, with the oldest patient being 98 years. Contrary to the specified trial criteria, about 4 percent of the patients were aged under 40 years, with the youngest being 10 years old, and 5 percent of patients received analgesics. Nevertheless, although these groups were included in the analysis, they were also considered separately.

Figure 1 shows that the number of men predominated in the group of those aged 40 to 59 years, whereas women predominated in the group of those aged 60 to over 80 years. Certain differences between the sexes also become apparent in relation to the calculated average age (men, 58 years; women, 63 years).

The duration of the disease exceeded nine years in 29 percent of cases, whereas 54 percent of the patients had had disease for between three and nine years and 17 percent had had it for less than three years. The frequency distribution of the affected joints (**Figure 2**) confirms the predominance of knee osteoarthritis, which is a finding of significance to social medicine; it also confirms the relatively frequent occurrence of degenerative spondylopathy.

For the differentiation of the degree of clinical severity, besides the baseline findings of joint pain and restricted movement, a radiologic classification was also required (only incipient or marked). As expected, older patients who as a rule had a longer history of the disease showed marked radiologic findings more often than others, with such changes being seen in a total of 56 percent of the patients (**Figure 3**).

Joint Pain. In the evaluation of the clinical findings, a qualitative assessment of the joint pain was made first. A

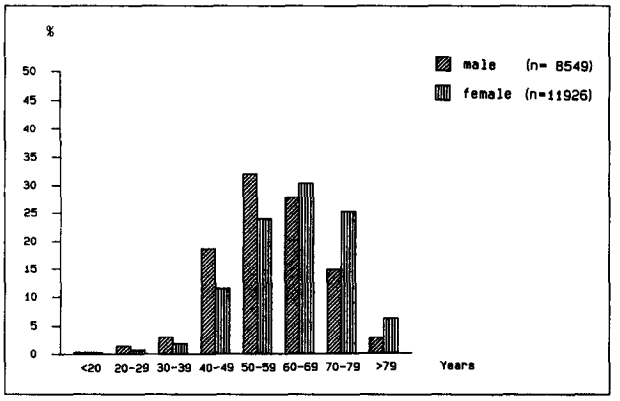

Figure 1. *Age distribution (histogram).*

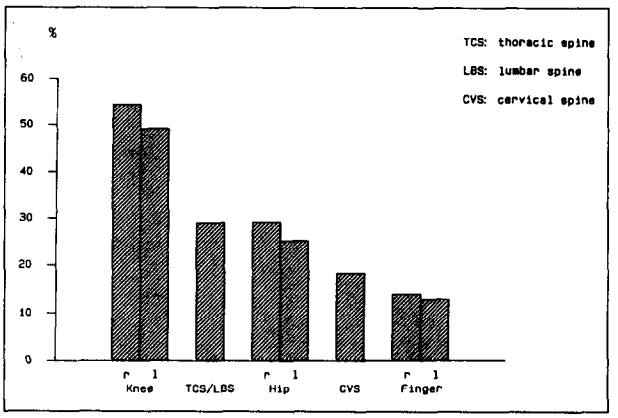

Figure 2. *Percentage of affected joints.*

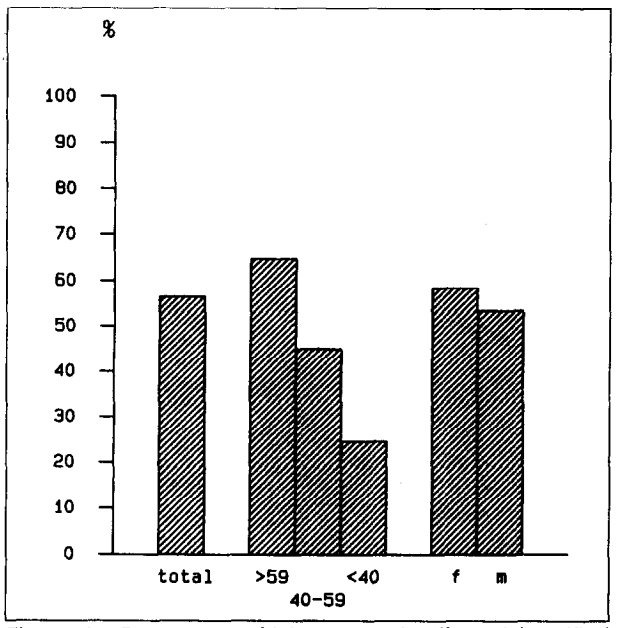

Figure 3. *Percentage of joints severely affected (stratified by age or sex).*

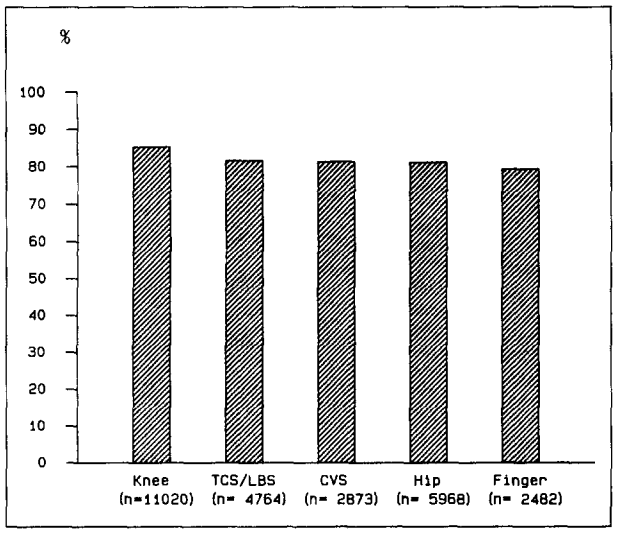

Figure 4. *Joint pain: percentage of patients with improvement from Week 0 to Week 8. TCS/LBS = thoracic spine/lumbar spine; CVS = cervical spine.*

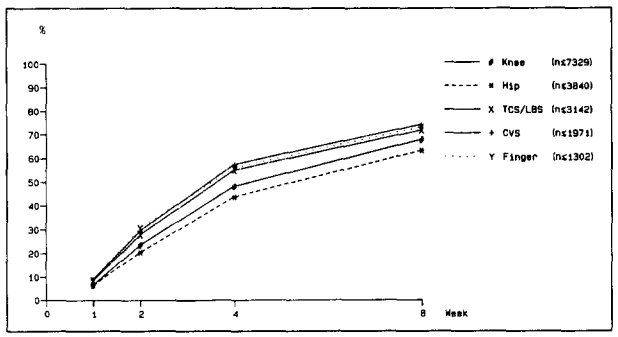

Figure 5. *Joint pain: percentage of patients with improvement of at least two points (subpopulation score 3 or 4 at Week 0). TCS/LBS = thoracic spine/lumbar spine; CVS = cervical spine.*

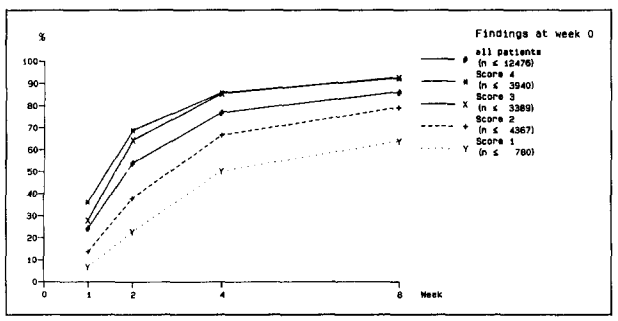

Figure 6. *Joint pain: percentage of patients with improvement stratified by pretreatment findings (knee).*

differentiation of the joint pain symptoms was specified, in accordance with the following scale as described by Steger [8]: 0 = no joint pain; 1 = pain following rest/morning stiffness; 2 = pain following exercise; 3 = pain during non-weight-bearing movement; and 4 = pain at rest/during the night or continuous pain.

An improvement in the joint pain status was assumed if existing symptoms of arthritic pain could be reduced, e.g., if nocturnal/continuous pain became exclusively pain following exercise.

Figure 4 shows that at all sites such an improvement could be achieved in approximately 80 percent of cases. **Figure 5** shows that more severe states of arthritic pain (scores of 3 and 4), considered separately according to location, could be improved by at least two points in a high percentage of cases. The course of the curves shows that already after four weeks of therapy, the majority of the patients may be considered to have sufficient improvement with a further increase by the end of the eighth week.

Considering gonarthritis, it is clearly seen that pain relief develops in a parallel fashion in the subgroups formed according to initial disease severity (**Figure 6**).

Subjective Well-Being and Functional Capacity. Poor subjective well-being was reported by 29 percent of the patients before the start of the treatment. After only four weeks, this percentage had decreased to four percent and after another four weeks, to 3 percent. There was a corresponding increase in the percentage of patients in whom subjective well-being was very good, from 5 percent at the beginning to 11 percent after four weeks and 16 percent after eight weeks of treatment (**Figure 7**).

The assessment of the functional capacity showed similar behavior, with the characterization "poor" being reduced from 37 percent to 6 percent and the characterization "very good" improved from 3 percent to 11 percent (**Figure 8**). In any event, at least a satisfactory functional capacity could be demonstrated in 94 percent of the patients at the end of the study compared with 63 percent before the trial.

Global Medical Assessment of Efficacy. At the end of the eight-week period of treatment, the investigator was to make a global assessment of the preparation with respect to its efficacy and tolerability using a four-point rating scale. On average, the groups of participating doctors (orthopedic surgeons, physicians, and general practitioners) assessed the efficacy as "very good" and "good" in 71 percent of cases (n = 19,993). The assessment "satisfactory" was made for 21 percent of patients, and the efficacy was described as "poor" for 9 percent of patients.

In patients with a radiologic degree of severity classified as "incipient," the global efficacy received a somewhat higher rating than in the major group with marked radiologic changes. No major sex-specific differences with respect to efficacy could be discerned.

When the efficacy of ademetionine was assessed according to age groups, it was found to have a very good or good effect in 75 percent of those in the group aged 40 to 59 years; the corresponding percentages for the group of those aged under 40 years and also for the group of those aged over 59 years were 78 percent and 67 percent, respectively.

The global medical assessment of the efficacy also showed that even with a duration of the disease in excess of nine years, a good or very good effect can still be expected in 63 percent of the patients. As expected, the global medical assessment did not show any relevant differences in efficacy between patients who had received antirheumatic therapy before the trial and those who had not.

Tolerability. Considering the tolerability of ademetionine, it is significant that within the treatment period, no serious drug-related adverse effect could be observed. This fact indicates a very high level of drug safety in the field of antirheumatics.

Accordingly, the treatment was discontinued because of side effects in only 5.2 percent of cases. In relation to the relatively long duration of the trial, this figure is to be classified as rather low and, on the basis of the fact that discontinuations of therapy mostly occurred in the first and second weeks (47 percent due to side effects), can be brought into a relationship with the relatively high tablet loading, especially since treatment was only rarely (16 percent) discontinued after the fourth week. In another 7.1 percent of the patients, the treatment was discontinued for various reasons not connected with the occurrence of undesirable side effects, including 2.3 percent because of a lack of efficacy. Other reasons given fairly often for the discontinuation of therapy were that the patient did not reappear for further follow-up, or was discharged from medical treatment. Also, admissions to the hospital in connection with other diseases led to premature discontinuation in some cases.

Side effects (moderate or severe) were reported by 21 percent of the patients participating in this trial. Most of these symptoms were related to the gastrointestinal tract and could be included among the so-called non-specific side effects also shown in other investigations, with shorter times of observation than in this clinical trial (three or four weeks versus eight weeks) [9].

The concluding assessment of the tolerability of the drug by the physicians resulted in 87 percent describing the tolerability as good and very good, and in 8 percent and 5 percent, respectively, describing it as moderate and poor (**Figure 9**). Fifteen deaths were reported in these 20,641 patients during the study; deaths were above all due to myocardial infarctions and cerebrovascular accidents. All deaths appeared to be explained by other factors and were not related to the administration of ademetionine.

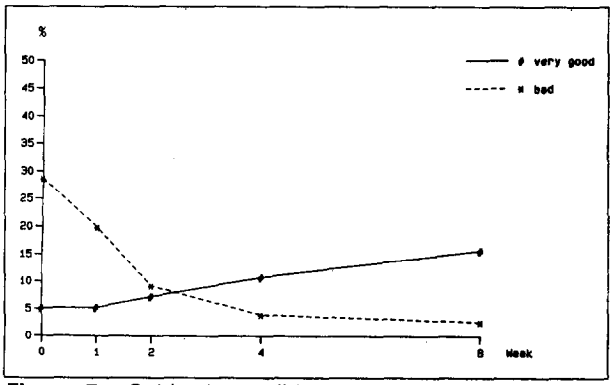

Figure 7. *Subjective well-being: percentage of patients feeling very well or poorly at various time periods (n = 20,369 or less).*

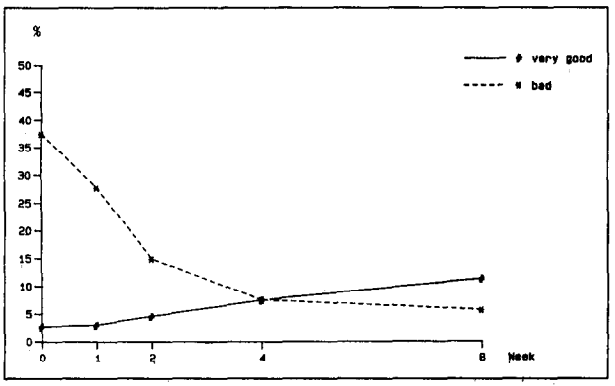

Figure 8. *Functional capacity: percentage of patients with very good or poor functional capacity at various time periods (n = 19,972 or less).*

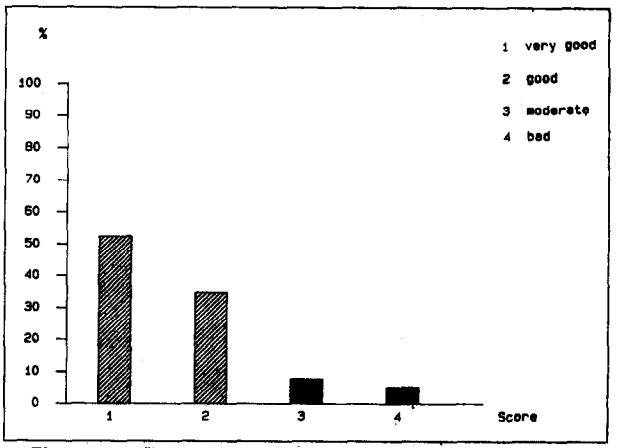

Figure 9. *Tolerability of the drug: global assessment.*

COMMENTS

On the basis of the controlled trials carried out thus far, the treatment of degenerative joint diseases with an endogenous active substance, which has many different biochemical effects [10], and the mechanism of action of which in the investigated indication has not yet been fully elucidated, represents a valuable addition to the possibilities of drug therapy [11]. The data presented herein from a broad multi-center trial confirm the results that have mainly been obtained from clinical studies under in-patient conditions. In contrast to the controlled trials conducted so far, under conditions of general practice, a verifiable reduction in the arthritic symptoms is generally not to be expected until after 14 days. Since it has already been observed by other investigators [12], the full effect develops at the earliest after four weeks of treatment. With long-term therapy (two years) in a dose of 200 mg twice a day, however, a further improvement was seen in the clinical scores even after an initial period of several months [12].

The delayed onset of efficacy means that under general-practice conditions, a good doctor-patient relationship is essential, especially in arthritic patients with acute and severe symptoms, in order to tide them over the first few weeks. Here concomitant therapeutic procedures (physical therapy, among others) and also additional analgesic medication are indicated. The trial protocol did not allow any additional analgesic medication. This evaluation shows that the inclusion of these restrictions on other analgesics was correct, because the duration and dose of analgesic drug therapy cannot be documented in a standardized way for large numbers of cases, and an assessment of efficacy is made more difficult.

As expected, the group of patients who had been previously treated with antirheumatic drugs up to just before the start of treatment with ademetionine did not show results that were any different from those for patients not treated directly before the trial.

PROSPECT

Patients with painful degenerative joint diseases make up a large contingent in the clientele of the physician in general practice and, as a rule, they are treated by "polypragmacy" [13]. The acute symptoms can be controlled relatively rapidly with nonsteroidal antirheumatics of the prostaglandin synthesis inhibitor type. Continuous drug administration is necessary in a large number of cases with recurrent symptoms or chronic joint impairment.

Treatment with nonsteroidal anti-inflammatory drugs entails particular health risks and limited tolerance in such cases. Certain groups of patients (asthmatic patients, those at risk for hemorrhage, persons with allergic diatheses, among others) cannot be satisfactorily treated by such drugs in any case. In addition, with the antirheumatic treatment available to date—as with any drug therapy—there are patients in whom there is no response to conventional medical treatment. With a number of nonsteroidal anti-inflammatory drugs, a harmful effect on cartilage metabolism has also been demonstrated in experiments performed in animals [14]. The indications obtained so far that ademetionine has a positive influence on cartilage metabolism currently form the subject of intensified investigations.

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