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Compliance and long-term effect of azathioprine in 65 rheumatoid arthritis cases

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SUMMARY Azathioprine has been used in our unit as a third line disease modifying drug (DMD) since 1969. In 65 patients with severe rheumatoid arthritis (RA), [45 females and 20 males, mean age 55·2 years (32 to 76), mean duration of disease 14 years (1 to 41)], azathioprine was given in an average dose of 1·5 mg/kg body weight/day for a mean duration of 33·4 months (range 1 to 108).

The mean follow-up was five years. One hundred and eighty-four patient years of treatment with azathioprine were observed. After three months' treatment, significant subjective and objective improvement was observed in 65% of the cases. This improvement remained in 29 cases who received continuous treatment for two years. In 12 of the 20 seropositive RA cases, a reduction of at least three dilutions in the rheumatoid factor titre was noted. In the 24 patients who were corticosteroid dependent, the dosage of steroids could be reduced by 35% and in four steroids could be stopped completely. Compliance after two years (n=54) was still 67%. Azathioprine treatment had to be stopped in 23 patients because of ineffectiveness in nine and adverse effects in 14. In three cases (4·6%) a malignant tumour occurred: one lymphoma and two adenocarcinomata. Low dose azathioprine therapy was shown to be useful as a third line disease modifying drug in RA without an increase in oncogenic risk. Compliance for azathioprine was found to be very satisfactory compared to other drugs.

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Since the introduction in 1951[106] of immunosuppressants in the treatment of rheumatoid arthritis, several studies have shown that immunosuppressive drugs can induce a measurable improvement in the inflammatory process.[18 34 38 56 69 95 109 113 177 214 225 237] Although the mechanism of action is still unclear, these agents have been used extensively in recent years. In our unit, azathioprine has been in use since 1969, and is considered as the third line 'disease modifying drug' after gold salts and D-penicillamine. In this retrospective study, the long-term effect, compliance and adverse effects of azathioprine have been evaluated in 65 patients who received the drug in the past decade.

Patients and methods

Sixty-five patients with classical rheumatoid arthritis, according to the American Rheumatism Association (ARA) criteria, were entered into the study. The characteristics of the patients are shown in table 1.

There were 20 men and 45 women, with ages ranging from 32 to 76 years (mean 55·2 years), and the average duration of rheumatoid arthritis was 14 years (range 1 to 41 years). The mean starting dosage of azathioprine was 1·5 mg/kg/day. Dosage was adjusted during the course of the disease according to clinical response. This study covers 184 patient treatment years, with an average duration of 33·4 months (range 1 to 108) of azathioprine therapy.

Treatment before azathioprine is listed in table 2. Most of the patients had had a course of gold, antimalarials or D-penicillamine treatment before azathioprine was started. Gold, antimalarials or D-penicillamine were discontinued before starting azathioprine. Fewer patients were treated with D-penicillamine since this drug was introduced several years after azathioprine in our unit. In patients receiving steroids and/or depot-ACTH, an attempt was made to reduce the dose as much as possible.

TABLE 1 *Characteristics of 65 patients treated with azathioprine*

Male/female	20/45
Mean age	55·2 yr (32–76)
Seronegative/seropositive	17/48
Mean duration of disease	14 yr (1–41)
Mean dosage of azathioprine	1·5 mg/kg/day
Mean duration of therapy	33·4 mth (1–108)
Mean duration of follow-up	5 yr
Total patient treatment years	184

TABLE 2 *Therapy before azathioprine*

Gold salts	41
Antimalarials	23
D-penicillamine	15
Prednisone	8
Depot-ACTH	12
Prednisone+ACTH	4

All patients continued the treatment with salicylates or non-steroidal anti-inflammatory drugs (NSAID), which they were taking when azathioprine was started.

The indications for azathioprine therapy are shown in table 3. Azathioprine was started, in most cases, because of failure of, or adverse effects to, 'classic therapy': gold, chloroquine or D-penicillamine. In 14 patients treatment was given in order to reduce corticosteroid dependency, and in six to control systemic involvement such as pericarditis or vasculitis. Each patient was seen at regular intervals at the outpatient clinic where the following assessments were made: subjective status (better, unchanged, worse), morning stiffness (hours) and clinical examination with special attention to the joint status. Laboratory tests performed at each visit included blood counts, sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, serum protein electrophoresis, liver function tests and urine analysis. The activity of the rheumatoid arthritis, as described in the charts, was defined by the following clinical activity scores, which were designed for retrospective studies.[205]

Grade 0 (remission)—no morning stiffness, no persistent joint pain, tenderness or swelling.

Grade I (mild RA)—persistent joint pain without morning stiffness, joint tenderness or swelling.

Grade II (moderately active RA)—presence of joint pain, tenderness and swelling and morning stiffness <120 minutes.

Grade III (severe RA)—persistent moderate or marked articular tenderness and swelling, associated with warmth and/or erythema and morning stiffness >120 minutes.

When charts were incomplete because of failure to attend during the last year, or death, information on the patient's condition, or cause of death, was sought from the family physician.

TABLE 3 *Indications for azathioprine therapy*

Failure of 'classic' therapy	30
Adverse reactions to 'classic' therapy	15
Corticosteroid dependency	14
Systemic involvement	6

Results

THERAPEUTIC EFFECTS

After three months of therapy 42 (65%) of the 65 patients had improved subjectively, morning stiffness had decreased in 42 (65%) and the number of swollen joints had reduced in 46 (70%).

To evaluate the long-term effect, a group of 29 patients who were treated for at least 24 months were selected for study. The results for this group who tolerated the drug are shown in table 4. Subjective improvement occurred in 21 (72%) after three months. This effect lasted for 24 months and was confirmed by improvement in the clinical findings; morning stiffness, number of swollen joints and ESR decreased significantly. The titre of the latex test decreased by three or more tube dilutions in 12 of 20 seropositive patients after 24 months. There was no significant change in haemoglobin levels, CRP or albumin/globulin ratio.

In 24 cases who were dependent on corticosteroids, it was possible to reduce the dosage by approximately 35%, and in four steroids could be stopped completely. The response of systemic involvement (two vasculitis, two pericarditis, one

TABLE 4 *Clinical outcome of 29 RA patients receiving azathioprine for 24 months*

	0 months	*3 months*	*6 months*	*12 months*	*24 months*
*Subjective					
Improvement	—	72	71	75	72
Unchanged	—	20	17	21	16
Worse	—	8	12	4	12
*Clinical activity grade					
0	0	0	4	11	11
I	13	30	46	30	39
II	45	52	50	59	39
III	42	18	0	0	11
Morning stiffness (hours)					
Mean±SD	2·3±1·3	1·6±1	1·7±1·2	1±1	1·3±1·2
p†		p<0·05	NS	p<0·001	p<0·01
No of swollen joints					
Mean±SD	6·3±3·5	4·5±2·6	3·6±2·9	4±3	3±2·1
p†		p<0·02	p<0·01	p<0·02	p<0·01
ESR					
Mean±SD	69±33·3	53±23·6	50±19·6	52±28·7	40±24·4
p†		p<0·001	p<0·01	p<0·01	p<0·001

*Percentage of patients assessed.
†Compared to the initial value using the paired Student's *t* test.

pleuritis, one Felty's syndrome) was good in all six cases.

COMPLIANCE

In order to assess the long-term effects and tolerance of azathioprine, compliance to treatment with azathioprine was evaluated in the 54 patients who started their treatment two years before completion of this study. A compliance study may give important information on therapeutic benefit since a drug which does not adequately relieve pain, or which causes intolerable side-effects, will be discarded by the patient. After two years, 36 (67%) patients were still continuing azathioprine therapy.

The figure compares the drop-out curve presented as life table survival curve for azathioprine with those of gold, D-penicillamine, hydroxychloroquine and levamisole, as published by Husain and Runge.[96] Compared to the compliance for other disease modifying drugs, azathioprine scores very well.

WITHDRAWALS AND ADVERSE EFFECTS

Twenty-three (35%) of the 65 patients were withdrawn, nine because of inadequate therapeutic response and 14 because of untoward effects which were: gastrointestinal disturbance in six cases, bone marrow suppression (leucocytes <3500, thrombocytes $<10^5/mm^3$) in seven cases and liver function disturbance in one case.

Thirty-eight (58%) of our patients experienced side-effects mainly in the initial three months of therapy (table 5).

In three cases a malignant tumour occurred: an undifferentiated lymphoma of the stomach 3·5 years after start of treatment in a 54-year-old man with Felty's syndrome (the patient is still alive and well seven years later); one adenocarcinoma of the stomach in a 65-year-old female 6·5 years after stopping 1·5 years' treatment with azathioprine (patient is still alive and well ten years later); and one cystadenocarcinoma of the appendix in a 66-year-old female two years after stopping seven years of azathioprine treatment.

Sixteen patients died and the causes of death are shown in table 6. The average age of death was 64·8 years (range 52 to 73).

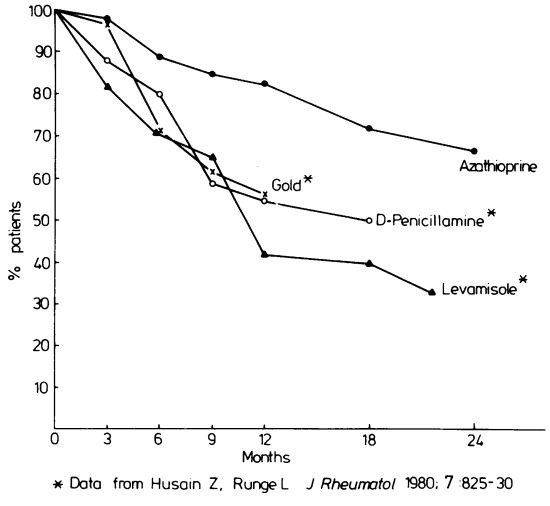

FIGURE *Patient compliance: disease modifying drugs (DMD).*

TABLE 5 *Untoward events in 38 of 65 patients on azathioprine*

GI disturbance	16	(25%)
Bone marrow suppression	16	(25%)
Infections	6	(9%)
Stomatitis	3	(5%)
Haematuria	6	(9%)
Skin rash	2	(3%)
Liver function disturbance	2	(3%)

Discussion

The results of our study are in accordance with those of others.[18 38 56 95 109 177 225] After three months of azathioprine treatment, with an average starting dose of 1·5 mg/kg/day, the majority of our patients, unresponsive to conventional therapy, showed evidence of improvement by subjective, clinical and laboratory criteria. In a group of patients who

TABLE 6 *Cause and age of death of 16 patients who died during follow-up period*

No	*Age*	*Sex*	*Cause of death*	*Duration of therapy (yr)*	*Interval between termination of therapy and death (yr)*
4	69	M	Postoperative complication	5	2
	60	M	Postoperative complication	9	0
	67	M	Postoperative complication	3·2	0
	64	F	Postoperative complication	4·5	4·5
4	71	F	Cardiovascular disease	0·75	2·5
	69	F	Cardiovascular disease	1·5	6
	67	M	Cardiovascular disease	6·5	0
	64	F	Cardiovascular disease	3	0
2	73	F	Cachexia	4·5	0
	63	M	Cachexia	1	0
2	68	F	Sepsis	2·5	0
	76	F	Sepsis	3	7
1	64	F	Malignancy	7	2
1	64	F	Diabetes	3	0
1	52	M	Suicide	3·5	0
1		F	Unknown	0·5	—

tolerated the drug for a long period, this improvement continued for at least two years. Except for sedimentation rate and rheumatoid factor, no important changes in biochemical parameters of inflammation were observed.

A moderate corticosteroid sparing effect was also observed. The clinical response observed in this retrospective study is similar to other studies. Urowitz *et al*[225] treated their patients for 24 weeks and found that, after 12 and 24 weeks, a significant clinical improvement occurred in more than 80% of their patients, independent of the dose of the drug taken. Laboratory evaluation revealed no important changes. Hunter *et al*[95] followed their patients up to 40 months; the initial improvement at 16 months continued until 40 months. Biochemically they found a decrease in the latex titre, ESR and immunoglobulin level. Pinals[177] treated his patients for at least 20 weeks and observed clinical improvement in 56% of his cases. Sedimentation rate did not change significantly, but the dose of corticosteroids could be reduced in seven of the 17 patients.

Dwosh *et al*[56] compared azathioprine with gold and chloroquine and found significant improvement in all three groups after 12 and 24 weeks. The latex titre fell significantly in the azathioprine and gold treated groups, but ESR rose in the azathioprine group after 12 weeks' treatment, despite continued clinical improvement. Berry *et al*[18] compared azathioprine with D-penicillamine in a one-year study and found equal efficacy of both drugs (70%). ESR and latex titre fell in both groups. Currey *et al*[38] compared azathioprine with gold and cyclophosphamide and observed a comparable improvement in the three treatment regimens. The ESR fell in the three groups, rheumatoid factor did not change and steroid requirements tended to fall.

The higher 'compliance' with azathioprine compared to other disease modifying drugs[96] may be explained by three facts: as a measure of efficacy it is in accordance with the observed therapeutic response; since it is a toxic drug, the follow-up of patients is generally more intensive, which has a positive effect on patients' motivation; patients know that azathioprine is, more or less, the 'last chance' drug in controlling their disease. Nevertheless, 35% of our patients were withdrawn from azathioprine therapy, this being higher than the 18 to 32% reported in the literature. Adverse reactions were frequent (58%), but led to discontinuation of treatment in only 21%. Most important were gastrointestinal disturbance and bone marrow suppression, the latter being reversible in all cases. The frequency of untoward events in our study is comparable with the mean frequency in the studies mentioned above.[18 38 56 95 109 177 225] Only haematuria, observed in six cases, has never been associated with azathioprine and is probably the result of other factors (NSAID, infection, cyclophosphamide).

Malignancy occurred in three patients (4·6%). Pinals[177] reported an incidence of 8% and Lewis *et al*[125] 4%, which was lower than in patients not treated with immunosuppressants (10%), suggesting that an altered immune status of RA patients[81] might facilitate oncogenesis. Immunosuppressants may play a role in tumour induction by chromosomal damage[95] or other mechanisms. According to published reports, alkylating agents are much more suspect than antimetabolites.[108 154 184]

In our study 16 patients died during follow-up, mainly because of cardiovascular disease and postoperative complications (table 6). We assume that the high mortality rate is the result of the lower life expectancy of rheumatoid arthritis patients of this age group (52 to 73 years, mean 64·8 years).[33 102 125 182 219] In only two cases is it possible that there was a causative relation between treatment and death (that is, infection and neoplasia).

One can confirm that azathioprine has an important antirheumatic activity but, considering its toxicity and potential oncogenic risk, its use should be reserved for the specific indications of:

(1) failure of conventional therapy in active rheumatoid arthritis;
(2) 'malignant' forms of rheumatoid arthritis; and
(3) corticosteroid dependency.