Rheumatoid arthritis: treatment with azathioprine (IMURAN (R)). Clinical side-effects and laboratory abnormalities

J K WHISNANT AND J PELKEY

From the Immunology Section, Department of Clinical Investigation, Burroughs Wellcome Co, USA

SUMMARY A retrospective review of the literature has been carried out to determine laboratory abnormalities occurring in patients with rheumatoid arthritis (RA) treated with azathioprine, in order to establish a profile for this agent in the treatment of this disease.

A total of 542 patients in 24 studies, reported in the literature, were given a range of doses of azathioprine for up to four years. Fifteen percent of patients were withdrawn because of toxicity. The two major toxic effects were gastrointestinal symptoms and alteration in blood counts. Clinically significant leucopenia (less than 2500/mm³) occurred in 14 of the total of 93 patients reported to have developed leucopenia. Some adverse reactions, which would have been expected from the use of azathioprine in other diseases, were uncommon, namely significant infections, hepatotoxicity and pancreatitis. Adverse experience with azathioprine in rheumatoid arthritis compares well with other slow-acting, or disease modifying, drugs.

* * * * *

Immunosuppressive therapy of rheumatoid arthritis (RA) with the thiouracil azathioprine (IMURAN (R)) has been reported since 1965. The initial experiences with this drug stimulated some enthusiasm and there were 11 publications in the period 1965–1970. In the next five years (1971–1975), the problems of significant haematological toxicity and the possibility of malignancy in renal transplantation patients treated with azathioprine caused concern, so that less investigation and interest was evident during these years. Major studies were reported again in 1976–1977 and some of these, especially those by Balken, Berry et al, Dwosh et al and Goebel et al, stimulated re-evaluation of the place of azathioprine in the treatment of rheumatoid arthritis. A total of 24 studies published in the English literature, or available in translation, over an 11-year period is now available for review to assess the composite adverse experience with azathioprine in this non-transplant disease category.

Methods of review

A composite azathioprine literature listing, including computerised reference banks, was first used to establish a primary literature data base. There are, as always, multiple citations which mention azathioprine for RA but which give no clinical data or patient reference to azathioprine or IMURAN (R).

TABLE 1 Twenty-four articles reviewed with year of publication, number of patients treated with azathioprine and concomitant therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Azathioprine</th>
<th>Other therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apostoloff et al</td>
<td>1974</td>
<td>9</td>
<td>Steroids, analgesics, antirheumatic agents</td>
</tr>
<tr>
<td>Balken et al</td>
<td>1976</td>
<td>41</td>
<td>Steroids, anti-inflammatory agents</td>
</tr>
<tr>
<td>Barnikol and Voriaender</td>
<td>1967</td>
<td>9</td>
<td>Antirheumatic</td>
</tr>
<tr>
<td>Berry et al</td>
<td>1976</td>
<td>33</td>
<td>Steroids</td>
</tr>
<tr>
<td>Bruckner et al</td>
<td>1969</td>
<td>6</td>
<td>Corticosteroids, asparin, prednisone</td>
</tr>
<tr>
<td>Cade et al</td>
<td>1976</td>
<td>18</td>
<td>Salicylates, steroids (1)</td>
</tr>
<tr>
<td>Currey et al</td>
<td>1974</td>
<td>44</td>
<td>Salicylates, aspirin, paracetamol</td>
</tr>
<tr>
<td>Denman et al</td>
<td>1970</td>
<td>5</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Dixon et al</td>
<td>1971</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Dodson and Bennett</td>
<td>1969</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Dwosh et al</td>
<td>1977</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Fricke and Deicher</td>
<td>1969</td>
<td>8</td>
<td>Steroids (1)</td>
</tr>
<tr>
<td>Goebel et al</td>
<td>1976</td>
<td>34</td>
<td>6-methyl-prednisolone, phenylbutazone, indomethacin</td>
</tr>
<tr>
<td>Khanna and Woodbury</td>
<td>1973</td>
<td>21</td>
<td>Aspirin, indomethacin</td>
</tr>
<tr>
<td>Levy et al</td>
<td>1975</td>
<td>49</td>
<td>Salicylates, steroids</td>
</tr>
<tr>
<td>Lorenzen et al</td>
<td>1969</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Mason et al</td>
<td>1969</td>
<td>27</td>
<td>Steroids, paracetamol</td>
</tr>
<tr>
<td>Mzsens and Broduer</td>
<td>1965</td>
<td>11</td>
<td>Steroids, 5-methyl-deltahydrocortisone, actinomycin-C</td>
</tr>
<tr>
<td>Pinals et al</td>
<td>1976</td>
<td>21</td>
<td>Corticosteroids (17)</td>
</tr>
<tr>
<td>Swannell and Coomes</td>
<td>1969</td>
<td>9</td>
<td>Steroids (9), ACTH (1)</td>
</tr>
<tr>
<td>Swannell and Kersley</td>
<td>1969</td>
<td>26</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Tausch et al</td>
<td>1970</td>
<td>73</td>
<td>Steroids (46)</td>
</tr>
<tr>
<td>Urowitz et al</td>
<td>1973</td>
<td>17</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Urowitz et al</td>
<td>1974</td>
<td>24</td>
<td>Salicylates</td>
</tr>
</tbody>
</table>

*Controlled study.
experiences, which were eliminated. A smaller, but significant, number of publications report fewer than five patients without comparison or control patient group information; these, too, were eliminated. The selected published studies included in this analysis are listed in table 1, with the numbers of patients and year of each publication. Some of the 24 studies were published more than once, but duplicate reporting of the same patient groups was consolidated in abstracting information. The authors' statements regarding diagnosis, or diagnostic criteria, were accepted. Patients included in these azathioprine studies were usually those with severe, disabling arthritis, unresponsive to conventional therapy. Careful attention was directed to eliminating the patients with diseases other than RA sometimes included in these reports.

All clinical toxicities and laboratory abnormalities included in each publication were tabulated. Summary profile sheets on each study were prepared, and these are available from the authors. It was not possible to impose a uniform grading system for severity of toxicities, except where specific haematological or other laboratory data were given. Results are given in terms of total percentage of patients with a specific toxicity. Particular attention was given to cases requiring withdrawal from treatment, to cases with life-threatening or fatal reactions and to toxicities occurring in control groups, where such were included (designated by asterisk in table 1). A detailed review of original patient records was conducted on four of the 24 studies: Urowitz et al,\textsuperscript{24} Urowitz et al,\textsuperscript{25} Levy et al\textsuperscript{13} and Cade et al.\textsuperscript{25}

Results

From this review of the literature, 542 patients could be studied (table 1). The most important side-effect of this antimetabolite thiopurine is its effect on white cell production manifest by peripheral leucopenia. The total incidence of haematological toxicity is illustrated in fig 1. Individual patient side-effects may have been multiple, and the percentage represented is the total for that individual toxicity. There were 142 haematological toxicity events reported in a total of 542 patients. Had all of these events occurred in separate patients, a total of 26\% of patients might have been affected.

Leucopenia of any degree was mentioned in 93 (17\%) of the 542 patients. Of these 93 patients, actual leucocyte values were reported in 67; these are summarised in fig 1. Fourteen patients were reported to have a leucopenia low enough to cause clinical risk

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Incidence of haematological adverse effects reported in 24 published reports of 542 patients receiving azathioprine (left). No of cases with degree of leucopenia as reported in patients on whom data are available (right).}
\end{figure}
Suppl p 46  Annals of the Rheumatic Diseases

(less than 2500/mm³). The majority of patients had
white blood cell counts between 2500 and 3500/mm³,
and an additional approximately 25% had counts
above 3500/mm³. There were an additional four
cases mentioned to have developed ‘neutropenia’,
but the degree of neutropenia was not specified.
Dis-continuation of therapy or withdrawal from a study
was uncommon as a result of haematological toxicity.

A review of the six studies published in 1976–197712 18 25 56 80 177 shows an incidence of
leucopenia of only 10%.

The haematological data from 108 patients in the
four studies reviewed in depth were similar to those
tabulated from the literature. The occurrence of mul-
tiple blood count abnormalities in one patient was
confirmed in these reviews. The study by Levy et al.,13 in
which a higher mean dose of azathioprine (2.9
mg/kg/day) was used, included a relatively high inci-
dence of leucopenia. A patient’s disease activity
measurements did not correlate with the degree of
leucopenia.

Gastrointestinal complaints were reported 103
times in the 542 patients, an incidence of 19% (fig 2).
Approximately 10% of patients had nausea and/or
vomiting, and gastrointestinal symptoms, not other-
wise specified, were reported in 6% of patients.
Other symptomatology was reported in less than 1% of
the total for each of the following: anorexia six
cases, ulceration four cases, diarrhoea two cases and
ulcer two cases. Two gastrointestinal toxicities,
reported in other investigational uses of azathiop-
rine, were not found in a significant percentage in
this review. There were only two reports of
hepatotoxicity, a significant problem in the use of
azathioprine in renal transplantation. There was only
one report of idiosyncratic, or ‘allergic’, pancreatitis
which has been reported in inflammatory bowel dis-
ease treated with azathioprine.

The review paid particular attention to patient
withdrawal and to prohibitive or life-threatening
reactions reported by the authors. Interruption of
azathioprine treatment, or withdrawal of patients,
was mentioned in relation to both haematological
and gastrointestinal toxicity. Eighty-one patients
were withdrawn because of drug-related adverse
reactions (15%).

Reports of infection (2.4%) in the context of this
immunosuppressive therapy were lower than might
have been expected, with most of these being bacte-
rial infection of a non-threatening nature. Five
patients, in three reports published before 1970, died

---

TABLE 2  Deaths or neoplasia reported in seven patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Azathioprine (mg/day)</th>
<th>Duration</th>
<th>Cause of death</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denman et al56</td>
<td>Rheumatoid arthritis</td>
<td>F</td>
<td>66</td>
<td>100</td>
<td>12 weeks</td>
<td>Bone marrow suppression</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Lorenzen et al139</td>
<td>Rheumatoid arthritis neuropathy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Few weeks</td>
<td>Pancytopenia</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Tausch et al111</td>
<td>Polymyositis</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>7 weeks</td>
<td>Amyloid nephritis</td>
<td>Pre-existing disease</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>8 weeks</td>
<td>Amyloid nephritis</td>
<td>Pre-existing disease</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>18 weeks</td>
<td>Interstitial nephritis</td>
<td>Pre-existing disease</td>
</tr>
</tbody>
</table>

Size of neoplasm

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Azathioprine (mg/day)</th>
<th>Duration</th>
<th>Cause of death</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cade et al19</td>
<td>Rheumatoid arthritis</td>
<td>F</td>
<td>44</td>
<td>75</td>
<td>4 years</td>
<td>Carcinoma of cervix</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Pinals175</td>
<td>Rheumatoid arthritis</td>
<td>F</td>
<td>59</td>
<td>100</td>
<td>9 months</td>
<td>Lung carcinoma</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>
during treatment. These five patients, plus two who developed malignancy, are summarised in table 2. The three patients reported by Tausch et al had renal dysfunction before immunosuppressive therapy, and it is doubtful that their deaths during treatment were caused by the drug.

The special concern about the induction of neoplasia in patients receiving this immunosuppressive thiopurine is the subject of other presentations in these proceedings. While we are aware of 18 individual case reports of malignancy in RA patients who have received azathioprine, the total number of patients treated is unknown. This review of 542 patients from 24 studies identified only two cases of carcinoma, an incidence of 0.4%. This may be compared with estimates of 0.6 to 2.6% malignancy in all patients with RA.

Discussion

The total frequency of adverse reactions in patients with RA treated with azathioprine compares favourably to the incidence of toxicity with other slow-acting, remission inducing agents. Physicians report unacceptable side-effects, or significant toxicities requiring withdrawal, in a significant percentage of patients and 1% of patients may develop life-threatening toxicity.

The six studies published in 1976 to 1977 show a lower incidence of leucopenia of 10%, and new treatment programmes are designed to follow recommendations for using lower doses of azathioprine (1.0 to a maximum of 2.5 mg/kg/day). Investigators have suggested temporary interruption of treatment, until white blood cell counts return to normal, and perhaps restarting the drug at half dosage. Dose modifications for controlling white counts, in patients taking 6-mercaptopurine or 6-thioguanine, are well known. However, in contrast to the treatment of malignant diseases, intentional suppression of peripheral leucocyte counts by progressive increase in dose is not considered to be the critical determinant of therapeutic response in RA.
Rheumatoid arthritis: treatment with azathioprine (IMURAN (R)). Clinical side-effects and laboratory abnormalities.

J K Whisnant and J Pelkey

Ann Rheum Dis 1982 41: 44-47
doi: 10.1136/ard.41.Suppl_1.44

Updated information and services can be found at:
http://ard.bmj.com/content/41/Suppl_1/44

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/