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Monitoring and Assessing the Safety of Disease-Modifying Antirheumatic Drugs

A West Midlands Experience

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Abstract

Background: Serious adverse events may occur from the use of disease modifying antirheumatic drugs (DMARDs) used to treat rheumatoid arthritis. We describe preliminary data from a regional surveillance scheme. Our aims were to identify a broad range of potential adverse events, to identify deficiencies in care and examine the management of common events in order to improve care.

Methods: Adverse events were sought by regular postcards to clinicians in the West Midlands region of the UK. Each reported case was carefully described and the opinions of at least three peer-reviewers were sought on cause-effect relationships, the potential for prevention and the appropriateness of management.

Results: Forty-four serious adverse events associated with DMARD use were reported between December 1999 and October 2001. Events included eight patients with malignancies, two with pancytopenia taking methotrexate, three with septic arthritis, and two with septicaemias. Fifteen cases have been peer-reviewed in detail, so far. At least two reviewers thought that eight events were related to DMARD use and that two were preventable. Agreement between pairs of reviewers was fair or moderate (weighted kappa 0.23–0.5).

Discussion: We have successfully implemented a regional system for identifying potential drug-related serious adverse events. A diverse range of potential drug-related events has been seen. Early analyses have highlighted the difficulties of determining cause-effect relationships between a drug and an event.

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, and disease modifying antirheumatic drugs (DMARDs; table I) are used in varying combinations to treat rheumatoid arthritis (RA). RA is multisystem disease that affects around 1% of the population. DMARDs are used early in the course of disease in order to improve the prospect of successful treatment and reduce the potential for morbidity due to irreparable joint damage.[1] Treatment with DMARDs may be given for many years, although sustained therapy beyond 3 years is most likely with methotrexate.[2] Most DMARDs appear to act through an effect on immune cells and many are immunosuppressive agents or antimetabolites. A variety of idiosyncratic and predictable adverse effects occur with DMARDs (table I). In order to detect drug toxicity

at an early stage, and to prevent serious consequences, drug therapy is monitored carefully. National and local guidelines for managing RA and monitoring DMARDs have been developed to ensure consistent approaches.[3] Monitoring schedules require pre-treatment screening investigations and repeated blood and urine testing when on therapy. For example, treatment with methotrexate requires a pre-treatment chest x-ray and routine haematology and biochemistry. Subsequently, blood is tested at 2–4 week intervals. Prolonged therapy, and the needs of monitoring for drug-related toxicity, places a substantial demand on patients and health services. Many have questioned the value of routine monitoring especially as serious adverse events are rare and are often unpredictable.[4] Nevertheless the quality of care of patients with RA is often judged, in local audits, by assessing adherence to monitoring schedules as laid down in monitoring guidelines. Few serious adverse events are encountered in such audits. Therefore, determining whether serious adverse events arise through a failure of adherence to monitoring, or any other preventable errors, is rarely feasible from such investigations.

Adverse drug reactions (ADRs) are common in hospitalised patients, and nearly a third are believed to be preventable.[5,6] However judgements as to whether clinical events are preventable are subject to great variation between reviewers.[7] ADRs are commonly under-reported to regulatory agencies through modern voluntary surveillance

Table I. Common disease modifying antirheumatic drugs and associated adverse events[a]

Drug	Common	Uncommon	Rare or very rare
Azathioprine	Nausea, rash, hypersensitivity, mouth ulcers	Leucopenia, infection	Lymphoma (long-term use)
Cyclosporin	Headaches, hypertension, renal impairment, depression, nausea, paraesthesiae, tremor, hypertrichosis, gingival hyperplasia, depression	Incipient renal failure, gout	Malignancy
Etanercept	Injection site reactions, upper respiratory tract infections, rhinitis, anti-DNA antibodies	Vasculitis	SLE, demyelination, aplastic anaemia, pancytopenia
Gold (sodium aurothiomalate or aurothioglucose)	Rash and pruritus, diarrhoea (especially with oral gold), mouth ulcers, thrombocytopenia, proteinuria	IgA deficiency, reduced Igs, neutropenia, cholestatic jaundice	Bone marrow aplasia, pneumonitis, exfoliative dermatitis,
Hydroxychloroquine (hydroxyurea)	Nausea, diarrhoea, rash, headache, dizziness, blurred vision	Myopathy or muscle weakness, tinnitus	Retinal toxicity
Infliximab	Hypotension, urticaria, headache, nausea, dyspnoea, sinusitis, anti-DNA antibodies.	Serious bacterial infections	SLE, unusual infections such as tuberculosis
Leflunomide	Hypertension, nausea, diarrhoea, mouth ulcers, abnormal LFTs, headache, dizziness, hair loss, rash.	Hypokalaemia, taste disturbance, tendon rupture, anxiety	Severe abnormality of LFTs, Stevens-Johnson syndrome, leucopenia ($<2.0 \times 10^9$/L), pancytopenia, agranulocytosis (very rare)
Methotrexate	Abdominal pain, nausea, diarrhoea, abnormal LFTs, neutropenia, macrocytosis, subcutaneous nodules, altered mood	Pancytopenia, pneumonitis, herpes zoster	Lymphoma, liver failure, unusual and severe infections
Penicillamine	Altered taste or loss of taste, nausea, mouth ulcers, rash or pruritus, proteinuria, thrombocytopenia (dose related)	Glomerulonephritis	Myasthenia, polymyositis, SLE, aplasia, neutropenia
Sulfasalazine	Nausea, rash, discoloured urine, leucopenia, fever, mouth ulcers, dizziness, oligospermia, raised MCV	Neutropenia, agranulocytosis, abnormal LFTs, reduced Igs	Pneumonitis

a Data are collated from a variety of sources, including drug data sheets. The term common indicates occurrence in approximately 1–10% of patients; uncommon 0.1–1%; rare 0.01–0.1%; very rare 0.01% or less.

Ig = immunoglobulin; **LFTs** = liver function tests; **MCV** = mean red blood cell volume; **SLE** = systemic lupus erythematosus.

systems, such as the Medicines' Control Agency's yellow card system in the UK and the US Food and Drug Administration's (FDA) adverse drug reaction reporting system (MedWatch), and this is more likely in multisystem disorders.[8,9] Serious and unusual events, however, are more likely to be reported by such postmarketing surveillance and case reports in journals.[10] The reasons for under-reporting include uncertainty as to whether the event was drug related, clinically unimportant events, well known events, and other factors such as time limitations, a complex reporting procedure, and a belief that a single case has limited significance.[11,12] These existing methods of surveillance for ADRs have a limited ability to identify potential ADRs that occur in chronic disease and with prolonged drug administration,[13] a matter of great relevance in RA, a disease that can affect many body systems. Determining cause-effect relationships for any drug is therefore much more difficult and likely to be subject to under-reporting.

In this report we describe preliminary experience of a region-wide survey of serious adverse events associated with DMARD use. Our survey was developed in order to identify any preventable factors associated with DMARD use. The goals of our long-term surveillance are, first, to foster collaboration and to provide an infrastructure for voluntary reporting of serious adverse events associated with DMARDs. Second, to develop a method of analysis based on structured peer-review. Third, to identify remediable factors and improve care through dissemination of our findings and by indicating areas for improving care. And finally, to analyse similar types of ADRs and examine clinical care in order to develop optimal management strategies for rarely encountered adverse events.

Methods

Surveillance

This project began with the presentation of an audit proposal to a sub-regional multidisciplinary postgraduate meeting of rheumatology health professionals in December 1999. The initial presentation proposed a model of surveillance and analysis based on the confidential enquiry into peri-operative deaths.[14] This was followed by a written proposal to all consultant rheumatologists in the West Midlands region. We emphasised in our communications that the audit goals were to learn from identified episodes and not to apportion blame, or to seek to compare hospitals or clinicians. Participation in the surveillance was entirely voluntary.

Participating clinicians were initially sent a monthly postcard asking whether a serious adverse event to a DMARD was seen in the preceding month. Return of the postcard was requested stating whether an event had been encountered, or not. Serious events were defined as follows: (i) drug causing death or life-threatening adverse event, or clinically important event resulting in hospitalisation; (ii) drug causing significant or persistent disability; (iii) drug resulting in, or associated with malignancy, or congenital or birth defect; (iv) leucopenia if <0.5 or $<2.0 \times 10^9$/L if associated with serious infection; or (v) thrombocytopenia $<50 \times 10^9$/L.

This definition is based on recommendations by the FDA with the addition of leucopenia and thrombocytopenia as defined above because of the potential seriousness of such reactions.[15] When a case was identified clinicians were asked to provide a local identification number but no other patient details. This was done to preserve anonymity and to comply with General Medical Council guidance and the current Medicines Control Agency's yellow card system in the UK.[16] Currently, postcards are sent to thirty-three interested rheumatology clinicians including consultant rheumatologists, senior trainees and clinical nurse specialists. Clinicians who chose not be involved in the study, at the outset, were not sent postcards.

Data Extraction

An anonymous detailed case report was prepared from medical records in each case by an experienced clinician. Two researchers then checked case details for completeness, accuracy and clar-

ity. The format of the report is standard and based on the FDA's reporting form for adverse events.[17] The rheumatologist in charge of the patient's case then completed a section on the case report in order that their perspective was made clear. Any factual errors in the case report were corrected, if necessary. The name of the clinician in charge was not revealed on the case report.

Analysis of Events

Case reports were sent without identifying the patient, their doctor, or their hospital to four senior rheumatologists (consultants or final year trainees) for peer review. Reviewers were drawn from the co-operating group of clinicians. This was done to encourage constructive involvement in the audit process and, we believe, their specialist knowledge, a familiarity with local approaches and healthcare systems increases the likelihood of identifying preventable errors. Four reviewers were chosen to ensure a spectrum of opinion and in the hope that this would improve reliability of peer assessments. The audit co-ordinating team took care to ensure that reviewers were drawn from a different unit to the one reporting an adverse event.

Reviewers were required to judge aspects of the case against their internal standards but were also directed to look at specific issues. A questionnaire, which had been piloted, was used which asked the reviewers to decide on a range of issues (shown with results in table II). Each item allowed categorical responses ranging from 3–5 defined categories. Each category had an appropriate descriptor. For example, whether the event was avoidable or not could be classified as 'definitely preventable', 'probably preventable', 'probably not preventable', 'definitely not preventable' and 'don't know'. Unstructured comments are invited at the end of the questionnaire.

Statistical Analysis

Responses of peer-reviewers were assessed for inter-rater agreement in pairs by use of kappa (κ) statistic. A weighted κ was calculated in order to allow for minor degrees of disagreement between reviewers. Responses classified 'don't know' were placed in the middle of ordered categories and weights for categories between two extremes were equally spaced.[18]

Results

Over 23 months the mean return rate for monthly postcards was 48%. Since July 2001 postcards have been sent out every 2 months and the most recent return rate (July/August 2002) was 51%. From December 1999 to October 2001, 44 patients with serious adverse events were reported. Preliminary data from events, and the associated DMARDs, are described in table III.

To date, 15 case reports have been peer-reviewed by at least three clinicians. Eight of the adverse events were believed to be at least 'probably related' to DMARD use by two or more clinicians. Two of these events were judged, at least, 'probably preventable' by two or more clinicians. In both cases two of four reviewers believed that there had been deviation from accepted norms of practice and, in one case, a patient who developed pancytopenia while receiving methotrexate, all four clinicians

Table II. Peer review of case reports: inter-rater agreement

Question		Weighted kappa
1	Was an adverse event present?	0.43
2	How serious was the event (whether drug related or not)?[a]	0.36
3	How probable was it that the adverse event was related to the drug(s)?	0.50
4	Was the adverse event due to an avoidable or a preventable error?	0.35
5	Was there a deviation from the accepted norms of practice that led to the presumed adverse event?	0.35
6	Was the management after detection of the presumed adverse drug event appropriate?	0.23

a Data for non-fatal categories.

Table III. Reported serious adverse events: description and associated disease-modifying antirheumatic drug (DMARDs)[a]

Type of adverse event	Total no. of events	Associated DMARD (no. of events)
Infections		
Pneumonia	3	Azathioprine (2), methotrexate (1)
Septic arthritis or osteomyelitis	3	Methotrexate (1), leflunomide (1), sodium aurothiomalate (1)
Shingles	3	Azathioprine (2), methotrexate (1)
Septicaemia	2	Azathioprine (1), methotrexate (1)
Tuberculosis	1	Infliximab (1)
Others (e.g. urinary tract, bacterial endocarditis, middle ear, meningitis)	5	Methotrexate (3), sulfasalazine (1), azathioprine (1)
Blood abnormalities		
Pancytopenia	2	Methotrexate (2)
Neutropenia alone ($<0.5 \times 10^9$/L)	1	Sulfasalazine (1), azathioprine (1)
Thrombocytopenia ($<50 \times 10^9$/L)	2	Sodium aurothiomalate (2)
Anaemia	2	Methotrexate (2)
Malignancy		
Definite or suspected lung cancer	3	Methotrexate (3)
Carcinoma of prostate	2	Methotrexate and cyclophosphamide (1), methotrexate (1)
Non-Hodgkin's lymphoma	1	Sodium aurothiomalate (1)
Other (thyroid adenocarcinoma, liver cancer)	2	Methotrexate (2)
Other events		
Shortness of breath	4	Methotrexate (4)
Leg amputation for osteomyelitis	1	Methotrexate (1)
Renal failure	1	Azathioprine (1)
Skin rash	1	Sulfasalazine (1)
Vasculitis	2	Sodium aurothiomalate (1), methotrexate and cyclosporin (1)
Liver failure	1	Methotrexate (1)
Deaths	4	Methotrexate and cyclophosphamide (1), methotrexate (2), azathioprine (1)

a Event numbers exceed patient numbers due to occurrence of more than one event in some patients.

judged that the management after occurrence of the event was inappropriate. However, overall agreement between reviewers was only fair or moderate, κ score range 0.23–0.50 (table II).

Discussion

We have described preliminary experiences with a voluntary, region-wide, audit of serious adverse events associated with DMARDs used for RA. Our surveillance method suffers from many of the same limitations that apply to voluntary reporting systems, such as the postmarketing yellow card system in the UK. First, these methods are not designed to estimate the frequency with which adverse events occur, and cannot determine the magnitude of any particular problem. For example, whether there is a greater risk of lung carcinoma in methotrexate-treated patients cannot be assessed from our survey. Only long-term cohort studies, with controls, have the potential for providing information on such issues. Secondly, under-reporting is common. For instance, units treating similar numbers of patients vary significantly in the number of patients reported to our audit. We believe this reflects under-reporting rather than differences in care between centres. In some cases misunderstanding about the scope of adverse events have come to light, especially when clinicians have doubted the cause of an event. An important feature of our methods is that of a monthly or bi-monthly prompt to clinicians, and involvement of reporting clinicians in analysis of ADRs.

We believe that such prompts improve the yield of ADRs.

Attributing causality cannot be readily assessed in our study. This was due, in some cases, to the nature of an event and in others because of the lack of a temporal relationship between an agent and the event. Therapeutic re-challenge is regarded as the 'gold-standard' for assessing causality. However this is often not feasible with serious events, unless the risks and benefits are considered very carefully and only if there are few therapeutic alternatives.[19] We relied on anonymous expert peer review to obtain a consensus on issues of causality and of quality of care. We believed that use of expert peer reviewers was a particular strength of our study as it allowed physicians with detailed background knowledge of disease processes and of DMARDs to make judgements based on a standardised case report. The degree of agreement between reviewers, in common with many such studies,[20] was modest (κ 0.23–0.5). Agreement may be improved by use of a more structured approach and we plan to explore this in future. However, it is known that disagreement is greater in situations where clinical judgement is necessary and in our case agreement was particularly poor when a poorly defined question was asked, for example when we asked: Was the management after detection of the presumed adverse drug event appropriate? It is clear from our early experiences, and from previous efforts, that the methods used in cause-effect judgements in relation to adverse drug reactions need to be improved.[20,21]

We did not feel that the methods of Naranjo and colleagues[22] for determining the probability of an ADR were suitable for several reasons. First, we found that many of the items on their scale were not relevant to the ADRs reported. For example whether there were previous conclusive reports of similar ADRs, the effect of the use of placebo, availability of blood levels of a suspected drug, and availability of 'objective evidence'. Second, one of the items listed, 'Did the adverse event appear after the suspected drug was administered?' would have led us to regard each case report as at least a 'possible' ADR, and would not have allowed reviewers to dismiss the possibility of an ADR. By contrast and third, we described earlier the problems of identifying possible ADRs in chronic disease with chronic drug administration. The criteria of Naranjo et al.[22] are weighted in favour of a temporal association between drug and ADR. We felt this was a disadvantage in our analysis.

One of our goals was to gain an insight into preventable factors. Few of the events analysed in detail were regarded as preventable but there is, so far, insufficient material for a detailed analysis of preventable factors and for important themes to emerge. Whether cases in which there are deficiencies in care are not being reported we are unable to say. We recognise that our methods allow only a limited analysis of the circumstances leading to each event and that, although cases are identified prospectively, case analysis is conducted through retrospective case review. Errors in care that have been identified by 'systems analysis' have involved detailed interviews with carers soon after an event, to identify remediable factors.[23] Nevertheless, our pragmatic methods allow for a wide range of potential drug-related adverse events to be examined than might be considered by regulatory agencies. For example, to our knowledge only two of these events were reported to the UK Medicines Control Agency using the yellow card system. A detailed case report is written for each event, often several months after reporting, with input from a clinician directly involved in patient care. A delay in assembling case details is advantageous in that relevant facts may emerge in time. For instance, clinicians may re-challenge patients with a potentially valuable drug after recovery from an adverse event. If it occurs, re-challenge allows for a more definitive judgement about ADR-drug relationships.

In summary, we have shown that it is feasible to improve the identification of adverse drug reactions associated with DMARDs by creating a network of interested local clinicians. Clinician inter-

est is maintained by direct involvement in analysis of events, regular local discussions and by crediting all participants with audit activity. Whether this activity will yield real benefits in improving patient care is, as yet, unknown. We have, at least, heightened awareness of possible drug-related adverse events and we hope we have generated interest in evaluating cause-effect relationships and in the methods of assessing quality of care when adverse events arise.

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