An Editorial Is a Golden Opportunity

What happened when sodium aurothioglucose (ATG) — a product previously available more than 70 years, that had been repeatedly proven effective for treatment of rheumatoid arthritis (RA), and was used across the world — was withdrawn without warning by the manufacturer? van Roon, *et al* describe their experience switching Dutch patients from ATG to aurothiomalate (ATM)[1].

The 2 products are similarly effective and have a similar spectrum of side effects[2]. There is little doubt that the mechanism of action is similar. The difference between ATG and ATM is in the fact that the former is dissolved in sesame oil and the latter in water based solution. ATG is thicker, and the oil vehicle is responsible for slower absorption of the drug and presumably improved side effect profile. When compared with ATM, ATG has a lower incidence of mucocutaneous reactions and almost no nitritoid reactions. The products appear otherwise to be interchangeable.

In Canada, ATG became available only after 1989; prior to this, patients used ATM exclusively or filled ATG prescriptions in the US. Between 1989 and 2001 our own gold clinic used ATG for about half our gold treated patients. All patients who had experienced nitritoid reactions and those who could not tolerate ATM due to mucocutaneous reactions were given ATG. Because of the known interaction between ATM and angiotensin-converting enzyme (ACE) inhibitors, which increases risk of nitritoid reactions, ATG became the preferred gold in patients taking ACE inhibitors[3,4]. In many of our patients, use of parenteral methotrexate is combined with gold therapy to optimize benefit from traditional disease modifying antirheumatic drugs (DMARD). The benefit and safety of this combination using ATG was demonstrated in a Canadian multicenter trial, for which the complete results will be published in 2005[5].

van Roon, *et al* switched 120 patients from ATG to ATM. That 16% experienced a new adverse reaction supports the older literature showing higher incidence of mucocutaneous reactions with ATM. Fourteen percent discontinued gold therapy after switching due to loss of effect and 3% due to remission. While in the majority, switching was successful, a total of 24% of patients who had previously been controlled on ATG discontinued ATM after switching.

The problems that led Schering to discontinue production of ATG received little publicity, very much in contrast to the recent withdrawal of Vioxx. For 6 months, ATG product was often back-ordered and not available, the company insisting that they were addressing production problems in their facilities. Patients began stockpiling because the drug supply was unreliable. Finally, and without warning to doctors, patients, or pharmacists, came the news that the product would no longer be produced. Authorities provided different explanations to me. Schering people explained that they could not meet strict quality control requirements of the US Food and Drug Administration (FDA) in their current facilities. FDA documents showed that Schering may have had problems with quality control due to the fact that many drugs were being produced using the same equipment, and because production processes had not been modernized to FDA standards. In a little-publicized but nevertheless public legal settlement, Schering agreed to a penalty of a US $500 million fine and agreed without admitting or denying allegations of the FDA, to discontinue an extensive list of products including ATG and triamcinolone hexacetonide, another drug we are missing in rheumatology[6]. Most listed drugs were considered by the FDA to be nonessential for a variety of reasons. Some drugs, which the FDA considered medically necessary, including ribavirin for hepatitis C and sterile water for use with etanercept, were excluded from voluntary discontinuation.

One rheumatologist working for the FDA explained to me that the availability of 2 alternative gold products, auranofin and ATM, as well as the availability of methotrexate and biological agents, was evidence that ATG was not an essential drug, not medically necessary.

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What followed the withdrawal of ATG was a shortage across North America of ATM because the producers of ATM could not build up production quickly enough to supply the whole market. This caused anxiety among caregivers and patients. In those who depended on gold to control their RA, we observed loss of disease control until supply problems were solved.

In 2005 there are 4 sources for ATM in North America, and one generic company is far along in the process of producing ATG. It is a guess that the current market for gold in North America might be 1%–2% of the DMARD market. This is a small percentage, but potential profit is enough to make the investment worthwhile for generic drug companies.

If ATG will soon become commercially available again, the work of van Roon and colleagues is more important, showing longterm safety in their cohort, tolerability, remission-inducing potential, and willingness of patients to switch when needed from one gold product to another. Over time many patients fail a DMARD due to loss of benefit or side effects. In a lifelong disease it is important to have choice in disease-controlling drugs and to have DMARD that are affordable as well as effective.

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