Characterization of Patients with Arthritis Referred for Gold Therapy in the Era of Biologics

JESSICA M. CHEUNG, DEBRA SCARSBROOK, and ALICE V. KLINKHOFF

ABSTRACT. ***Objective.*** To describe the clinical characteristics of patients referred for gold therapy and determine the reason for referral.

Methods. We conducted a chart review of patients referred for gold at the Mary Pack Arthritis Program, Vancouver, Canada, from July 2007 to July 2009.

Results. The sample included 69 female and 12 male patients. Diagnosis was rheumatoid arthritis (RA) in 71/81, psoriatic arthritis in 5, juvenile idiopathic arthritis (JIA) in 2, Sjögren syndrome in 1, undifferentiated polyarthritis in 1, and spondyloarthritis in 1. Twenty of 81 patients had received gold before: 15 were referred for a second course, 4 a third course, and 1 a fourth course. Ten of 81 patients were referred for gold as their first disease-modifying antirheumatic drug (DMARD). Seventy-one had received prior DMARD: 1 prior DMARD in 22 patients, 2 in 24 patients, 3 in 15 patients, and > 3 in 6 patients. Four patients had received prior biologic therapy plus 2 to 4 prior DMARD. Twelve of 71 received gold monotherapy, 56/71 received gold/DMARD combinations, and 3 received gold/biologic/DMARD combinations. Reasons for referral included failure of other DMARD in 54 patients, limited DMARD options in 50 (chronic liver disease in 34, sulfa allergy in 7, high alcohol consumption in 5, and planning pregnancy in 4), physician choice in 12, previous benefit from gold in 10, benefit of clinic support in 10, inappropriate for biologics in 7, patient choice in 4, and failure of biologics in 3.

Conclusion. The most common reasons for referral to gold clinic in 2007 to 2009 are failure of other DMARD and limited DMARD options due to underlying liver disease. (First Release Feb 15 2012; J Rheumatol 2012;39:716–19; doi:3899/jrheum.111097)

Key Indexing Terms:
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Gold has been used to treat rheumatoid arthritis (RA) since the 1920s[1,2,3]. A series of placebo-controlled trials in Europe and North America have provided evidence of gold's effectiveness and safety as monotherapy and when combined with other disease-modifying antirheumatic drugs (DMARD). In comparative studies, the efficacy of gold is similar to that of methotrexate (MTX). Since the mid-1980s, the use of gold has diminished worldwide due to multiple advantages of MTX, including cost, convenience, and safety concerns[4,5]. Gold is thought to reduce inflammation and modify the immune system by inhibiting macrophage, neutrophil, and lymphocyte responses and modulating levels of tumor necrosis factor (TNF) and other inflammatory mediators[1,3]. A recent study suggested that aurothiomalate increases the expression of a possible arthritis suppression gene, MAPK phosphatase 1[6]. Gold compounds in clinical use include parenteral gold sodium thiomalate and oral auranofin[1,2].

The current recommendation for patients with RA with low to moderate disease activity includes early treatment with traditional DMARD, particularly MTX, before proceeding to biologic agents[7]. American College of Rheumatology (ACR) recommendations for the management of RA emphasize the role of MTX and biologic agents but do not include a role for gold[8]. In contrast, EULAR guidelines address alternatives to MTX, including gold therapy, and reference high-level evidence for this position[9]. A 2002 survey of rheumatologists who were members of the Canadian Rheumatology Association revealed that MTX and hydroxychloroquine were prescribed by all rheumatologists for RA and sulfasalazine was prescribed by 98% of rheumatologists. Intramuscular gold was prescribed by 40% to 56% of rheumatologists whereas oral gold was rarely prescribed[10].

The Mary Pack Arthritis Program has operated monitoring clinics for RA DMARD, beginning with gold, since 1969. Currently, clinic monitoring is provided for patients taking gold, gold/DMARD combinations, and cyclosporine.

From the Faculty of Medicine, University of British Columbia, and the Mary Pack Arthritis Centre, Vancouver, BC, Canada.

J.M. Cheung, BSc, Faculty of Medicine, University of British Columbia; D. Scarsbrook, RN, Mary Pack Arthritis Program, Nursing; A.V. Klinkhoff, MD, FRCPC, Medical Director, Mary Pack Arthritis Programs, Department of Medicine, University of British Columbia.

Address correspondence to Dr. A. Klinkhoff, Mary Pack Arthritis Centre, 895 West 10th Avenue, Vancouver, BC V5Z 1L7, Canada. E-mail: alice.klinkhoff@vch.ca

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Monitoring is also provided for patients receiving parenteral MTX and infusion biologics when close monitoring is desired by the referring rheumatologist. From 2001 to 2011, the drug monitoring program served an average of 680 patients per year for ongoing monitoring; about 250 of these patients are taking gold and gold/DMARD combinations. Each year, there are an average of 40 new referrals for gold monitoring and between 30 and 50 discharges from the gold clinic.

We reviewed the medical charts of patients referred for gold during a recent 2-year period from July 2007 to July 2009 in order to describe the patient population and to identify the reasons for referral when biologics and other DMARD are available.

MATERIALS AND METHODS

We reviewed the medical charts of patients referred for a new course of gold at the Mary Pack Arthritis Center, Vancouver, Canada, between July 2007 and July 2009. Patients were identified using admittance data, but were not contacted. Patients referred for gold received injections of gold sodium thiomalate following a treatment protocol previously outlined in the METGO study[4].

The following demographic data were collected for each patient: date of birth, sex, diagnosis, year of diagnosis, and rheumatoid factor (RF) status. Medication management was recorded, including number of gold courses received since RA diagnosis, DMARD prescribed prior to and concomitantly with gold treatment, and duration on gold at the last visit in July 2009. A new gold course was defined by no receipt of gold for 8 consecutive months. "Concomitant DMARD" referred to any DMARD that was prescribed to a given patient while taking gold, and did not imply that the patient was taking all listed DMARD at the same time. The reasons for referral were determined from patients' medical history, correspondence letters between referring physicians, and other information from the medical charts. Reasons for referral were grouped into 8 categories: (1) failure of regular DMARD; (2) limited DMARD options; (3) failure of biologics; (4) inappropriate for biologics; (5) previous benefit on gold; (6) benefit from clinic support and monitoring; (7) patient choice; and (8) physician choice. Category 1 and 3 included patients with inadequate response, loss of effect, or side effects taking DMARD or biologics, respectively. Category 2 included liver disease (fatty liver, primary biliary cirrhosis, hepatitis B/C, and elevated liver enzymes), sulfa allergy, plans to conceive, and high alcohol consumption. Category 4 included patients with disease not severe enough for biologics, patients ineligible for insurance coverage of biologics, and contraindications to biologics. Data were analyzed semiquantitatively by calculating frequencies, and qualitatively by organizing reasons for referral into categories.

RESULTS

Eighty-one patients were included in the analysis, 10 of whom were referred for gold but chose not to start gold therapy. Demographic information and disease characteristics are shown in Table 1. At the time of admission to the gold clinic, the disease duration was < 2 years in 19 patients, 2 to 5 years in 19 patients, 6 to 10 years in 7 patients, 11 to 20 years in 19 patients, and > 20 years in 7 patients. RF was positive in 63 patients, negative in 13 patients, and unknown in 5 patients.

As of July 2009, 51 patients were referred for their first gold course and 20 patients had received gold previously. Of the latter, 15 were referred for a second course, 4 for a third course, and 1 for a fourth course of gold. Ten patients had received no prior DMARD. Twenty-two patients had received 1 prior DMARD, 24 patients 2 prior DMARD, 15 patients 3 prior DMARD, 6 patients > 3 prior DMARD, and 4 patients 2 to 4 prior DMARD, plus 1 or 2 prior biologic agents. Patients in the latter group had previously been treated with etanercept, adalimumab, or both, prior to referral to the gold clinic.

Table 1. Demographic and disease characteristics of patients referred for gold treatment.

Characteristic	No. (%)
Gender, n = 81	
Female	69 (85)
Male	12 (15)
Age, yrs, n = 71	
≤ 30	3 (4)
31–50	21 (30)
51–70	35 (49)
> 70	12 (17)
Diagnosis, n = 81	
Rheumatoid arthritis	71 (88)
Psoriatic arthritis	5 (6)
Juvenile idiopathic arthritis	2 (2)
Undifferentiated polyarthritis	1 (1)
Sjögren's syndrome	1 (1)
Spondyloarthritis	1 (1)
Disease duration, yrs, n = 71*	
< 2	19 (27)
2–5	19 (27)
6–10	7 (10)
11–20	19 (27)
> 20	7 (10)
Rheumatoid factor, n = 81	
Positive	63 (78)
Negative	13 (16)
Unknown	5 (6)

* Counts and percentages based on available data. Ten patients never started gold and thus disease duration and age at time of admission to clinic were not applicable.

Concomitant DMARD were not necessarily taken simultaneously as some patients failed various DMARD while receiving gold and changed to different gold/DMARD combinations. Details regarding gold/DMARD combinations and duration of gold treatment are included in Table 2. The 3 most highly subscribed gold/DMARD combinations were gold/plaquenil (20/71), gold/MTX/plaquenil (12/71), and gold/MTX (11/71). Twelve patients received gold monotherapy.

In descending order, the most common reasons for referral (Table 3) were failure of regular DMARD (54 patients), limited DMARD options (50 patients), physician choice (12 patients), previous benefit from gold (10 patients), benefit from clinic support and monitoring (10 patients), inappropriate for biologics (7 patients), patient choice (4 patients),

Table 2. Duration of gold treatment and concomitant disease-modifying antirheumatic drugs (DMARD) received during gold treatment.

Drug Treatment	No. (%)
Gold duration (mo) at last visit in 2009, n = 71*	
≥ 5	25 (35)
6 to 10	14 (20)
11 to 20	22 (31)
≥ 20	10 (14)
Concomitant DMARD, n = 71*	
None	12 (17)
1 DMARD	36 (51)
2 DMARD	18 (25)
3 DMARD	2 (3)
1 biologic	1 (1)
≥ 1 DMARD + biologic	2 (2)
Concomitant gold/DMARD combinations, n = 71*	
Gold alone	12 (17)
Gold + MTX	11 (15)
Gold + HCQ	20 (28)
Gold + SSZ	3 (4)
Gold + CyA	2 (3)
Gold + anti-TNF	1 (1)
Gold + MTX + HCQ	12 (17)
Gold + MTX + SSZ	2 (3)
Gold + MTX + LEF	1 (1)
Gold + MTX + anti-TNF	2 (3)
Gold + HCQ + SSZ	3 (4)
Gold + MTX + chloroquine + LEF	1 (1)
Gold + MTX + HCQ + SSZ	1 (1)

* Counts and percentages based on available data. Ten patients never started gold and thus disease duration and age at time of admission to clinic were not applicable. MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; CyA: cyclosporin A; anti-TNF: anti-tumor necrosis factor (includes etanercept, adalimumab, and/or infliximab); LEF: leflunomide.

and failure of biologics (3 patients). Some patients fit into more than one category. Category 2 was further separated into contraindications and allergies to other DMARD. Liver disease accounted for most of the patients in this category (34 patients), followed by sulfa allergy (7 patients), high alcohol consumption (5 patients), and women planning pregnancy (4 patients). Patients included in category 6 required close supervision, were noncompliant, or experienced anxiety about their condition and treatment.

Table 3. Reasons for referral to gold clinic (n = 81)

Category	No. (%)
1. Failure of regular DMARD	54 (67)
2. DMARD options limited due to:	50 (62)
Liver disease	34 (42)
Sulfa allergy	7 (9)
High alcohol consumption	5 (6)
Planned pregnancy	4 (5)
3. Failure of biologics	3 (4)
4. Inappropriate for biologics	7 (9)
5. Previous benefit on gold	10 (12)
6. Benefit from clinic support and monitoring	10 (12)
7. Patient choice	4 (5)
8. Physician choice	12 (15)

DMARD: disease-modifying antirheumatic drugs. Some patients fit into > 1 category.

DISCUSSION

A 1998 survey of Canadian and American rheumatologists revealed that Canadian rheumatologists favored gold more than their American counterparts for patients who failed MTX[11]. In the 2008 ACR recommendations regarding the use of DMARD (nonbiologic and biologic), gold was reviewed but not included in the recommendations. In their literature review, they confirmed that MTX, leflunomide, and sulfasalazine were contraindicated in patients with abnormal liver transaminases and hepatits B or C infection; and MTX and leflunomide were contraindicated in women who were currently pregnant or planning to conceive within 3 months or 2 years, respectively[8]. In our clinic, gold was a useful alternative for patients who had limited DMARD options, such as those who wished to become pregnant, had liver disease, or developed elevated liver enzymes taking other DMARD. Gold is safe to use in patients attempting to conceive or who are currently pregnant, and incidents of hepatotoxicity are rare[12,13]. Excessive alcohol consumption is another contraindication for MTX, and in our population 5 patients with high alcohol intake were identified. For patients with mild or moderate disease, it was considered beneficial to delay costly or inappropriate biologic treatment by recommending a trial of gold. An interesting subset of patients was referred for the benefit of the clinic environment and the associated medical supervision from a team that included nursing staff.

A limitation of our study is that while the reason for referral was obvious in most cases, bias or error may have been introduced in other cases where the reasons had to be interpreted from correspondence letters. Error in data collection could have been introduced by incongruities inherent in medical records. Some categories may have overlapped; it would be informative to survey referring physicians to identify why they recommended gold in a particular patient so that patients referred for gold due to "physician choice" could be assigned to a more specific category. Results are also reflective of patients at only one center.

Vancouver physicians have continued to refer arthritis patients for injection gold treatment. The most common reasons for referral from 2007 to 2009 were limited DMARD options due to underlying liver disease and failure of other DMARD.

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