Longterm Outcome of Treatment of Felty's Syndrome with Intramuscular Gold: Case Reports and Recommendations for Management

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ABSTRACT. ***Objective.*** To evaluate the incidence, complications, and course of Felty's syndrome (FS) in patients treated with intramuscular (IM) gold.

Methods. Retrospective chart review of all FS cases (1979 to 2003) was conducted in the Mary Pack Arthritis Centre (MPAC) gold clinic. FS was diagnosed if patients had rheumatoid arthritis (RA; American College of Rheumatology criteria) and persistent leukopenia [white blood cell (WBC) count < 4] in the absence of other known causes of leukopenia. Splenomegaly was not part of the inclusion criteria.

Results. Thirteen patients with FS were identified in the gold clinic population. The mean age at diagnosis of FS was 58.7 years and the mean duration of RA at time of diagnosis was 6.9 years. The weekly dose of gold ranged from 10 mg to 50 mg depending on tolerability. Gold therapy resulted in normalization of the WBC count in 9 of 13 patients. The mean time to normalization of the WBC was 40 weeks. Only one patient with FS had experienced recurrent infectious complications from FS, and this did not recur after gold treatment was initiated. No patient had vasculitis.

Conclusion. In our gold clinic population FS is a mild disease and is rarely associated with infectious complications. Gold is an effective treatment of FS. (J Rheumatol 2005;32:20–6)

Key Indexing Terms:
FELTY'S SYNDROME RHEUMATOID ARTHRITIS GOLD LEUKOPENIA

Felty's syndrome (FS) is a rare extraarticular manifestation of seropositive rheumatoid arthritis (RA). Diagnosis is based on the findings of unexplained neutropenia associated with RA. The traditional triad includes splenomegaly; however, FS is well known to occur in the absence of an enlarged spleen. Use of medical therapies including corticosteroids, gold, methotrexate (MTX), cyclosporine, recombinant granulocyte stimulating factor, lithium salts, parenteral testosterone, high dose intravenous gamma globulin, and leflunomide has been reported in small series and case reports[1-13]. The largest series of patients with FS included 20 treated with intramuscular (IM) gold during the years 1978–82[4]. Since then the management of RA has changed substantially. There are no controlled trials of FS treatment and there is no consensus on when and how to manage patients with this condition.

It is widely believed that effective treatment of RA is normally successful in ameliorating or preventing extraarticular features such as FS. Experienced rheumatologists claim FS is occurring less frequently and is less severe with modern disease modifying antirheumatic drug (DMARD) treatment. We review our experience with treatment of FS in a dedicated gold clinic and evaluate the incidence, complications, and management of FS. Based on this experience we recommend principles of management of neutropenia in patients with RA receiving potentially myelotoxic therapies.

MATERIALS AND METHODS

A retrospective chart review of gold clinic patients attending during the years 1979–2003 was performed. Patients are evaluated in the clinic about every 3 months, and laboratory and side effect data are collected prospectively according to an established protocol. Patient and disease characteristics, gold dose, duration of gold treatment, laboratory measures, and time to response of the white blood cell (WBC) count to treatment were extracted from the records.

The gold treatment regimen consists of weekly injections beginning with the test dose of 10 mg, followed by 25 mg, and subsequently 50 mg weekly. Thereafter, the regimen is predominantly a weekly injection schedule of 25 mg or 50 mg, depending on tolerability. Once the patient achieves the expected response or remission, the gold may be reduced to every 2 weeks. In the event of a sustained gold induced remission, intervals between injections may occasionally be gradually increased to monthly. If improvement in clinical and laboratory outcomes, and in reduced erosions, is not achieved on a biweekly regimen, weekly injections may be continued as maintenance therapy[14]. If there is a partial response to weekly gold, a second DMARD is commonly added. In the event of a side effect that is not serious, gold is held back until the side effect subsides, and then resumed at a 50% lower dosage. About 20% of our patients do not tolerate standard doses of gold, and in these patients we reduce the dose by 50% sequentially until a dose is reached to which the patient does not develop reactions[15]. Over time many patients are desensitized to the mucocutaneous side

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effects, and the dose of gold can be adjusted gradually upwards if needed to control RA[16]. Gold is not normally discontinued except for lack of effect after an adequate trial, or in the event of potentially serious side effects, such as thrombocytopenia, aplasia, pulmonary infiltration, hepatitis, or enterocolitis. Mucocutaneous side effects of gold, such as dermatitis and stomatitis, are so common that the protocol allows the nurse to make needed adjustments on a week by week basis; the physician evaluates the patient every 3 to 6 months, and more frequently when needed[16]. Proteinuria ≥ 500 mg/dl normally requires temporary discontinuation of gold. Once proteinuria has subsided, gold is reintroduced at 50% lower dosage.

FS was diagnosed in RA patients in the presence of persistent leukopenia (WBC < 4×10^3/μl) for 2 months with splenomegaly or bone marrow biopsy consistent with FS or when no other cause of leukopenia could be found. Viral infections and cyclic neutropenia were excluded by history, physical examination, and chart review. Potentially myelotoxic drugs were discontinued to observe the trend of WBC. Investigations to rule out infections were conducted based on clinical features at presentation such as fevers and cough. Ultrasound of the abdomen to assess for splenomegaly was done for the majority of patients suspected to have FS. If no splenomegaly was detected by physical examination or ultrasound, we proceeded to bone marrow biopsy. The diagnosis of FS was confirmed only if leukopenia persisted despite the discontinuation of myelotoxic drugs for at least 2 months and after ruling out other potential etiologies like viral infections and cyclic neutropenia. Good response to treatment was defined as normalization of the WBC count. Partial response to treatment was defined as increase without normalization of the WBC count. Failure was defined as no change in the total WBC count. The WBC count was chosen as the target measure because the clinic routine does not include differential counts at each visit.

Management of granulocytopenia. Because cytopenias may be caused by gold therapy and by other potentially myelotoxic therapies, the treating physician ordinarily sets in advance a target WBC count, below which gold treatment would be temporarily suspended. This target was roughly 30% lower than the presenting WBC count at time of FS diagnosis. In most cases this target was between 1.8 and 2.5. In cases where there was a drop in WBC below the target during treatment, gold was held back until the WBC count increased to the level of or above the target. Thus, the gold treatment course could be interrupted for one or several weeks in order to assure that a downward trend representing gold toxicity was not evolving. In no patient was gold discontinued due to progressive neutropenia.

RESULTS

Between 1979 and 2003, 13 patients with FS attended the gold clinic at the Mary Pack Arthritis Centre. Patient and disease characteristics are included in Table 1. Twelve of 13 were female. Twelve of 13 were rheumatoid factor (RF) positive and the RF status of one was not documented. Mean age at diagnosis of FS was 58.7 years and mean duration of RA was 6.9 years. FS was present at the time of diagnosis of RA in 2/13 (Patients 6 and 7). No patient had vasculitis. One had experienced recurrent infectious episodes prior to treatment of FS with gold (Patient 3). Seven of 13 had splenomegaly, identified on ultrasound in 5 and physical examination in 2 (Patients 3 and 5). Ultrasound was done in 9 of 13 patients. Four underwent bone marrow biopsy for diagnosis (Patients 2, 4, 5, and 10). Bone marrow showed normal cellularity with maturation arrest. This was felt to be consistent with the diagnosis of FS. Three patients were considered to have FS on a clinical basis (Patients 6, 8, and 12), but did not have splenomegaly on ultrasound or physical examination and did not undergo bone marrow biopsy. No infectious etiology was identified in these patients. The leukopenia persisted despite the discontinuation of myelotoxic drugs. Adverse drug reactions and cyclic neutropenia were excluded. FS was felt to be the most likely diagnosis in these patients. Of these 3, Patient 6 had no prior use of DMARD and FS was part of the presenting features of RA. Patients 8 and 12 had their DMARD discontinued (minocycline and sulfasalazine, respectively; plaquenil was not discontinued) for at least 2 months without normalization of WBC in this observational period. Patients 8 and 12 are still receiving gold therapy to the present time. They are considered partial responders.

Details of gold treatment and response are included in Table 2. In 8 of 13, IM gold was used to treat both FS and active RA. Five of 13 developed neutropenia early in the gold treatment course and were diagnosed with FS after starting therapy (Patients 1, 5, 9, 10, and 12). Two of 13 developed FS while undergoing treatment with MTX and were eventually switched to gold because of progressive decrease in neutrophil count while receiving MTX (Patients 2 and 11). In these 2 patients bone marrow biopsy findings showing normal cellularity with maturation arrest were felt to be consistent with FS rather than myelotoxic effects of MTX. Nine of 13 had a good response to treatment of FS measured in terms of normalization of the WBC count. The mean time to normalization of the WBC was 40 weeks (range 8–128 weeks). In 4 of 13 the WBC did not normalize; one of these discontinued gold due to thrombocytopenia after 22 months (Patient 5). Another discontinued gold because of gold dermatitis after 9 months (Patient 13). Two patients who did not normalize the WBC count continue receiving gold to the present time after 34 and 50 months, with good control of RA disease activity (Patients 8 and 12). In all patients the dose of gold ranged from 10 to 50 mg weekly depending on tolerability. Duration of gold treatment ranges from one to 14 years in patients who continue gold and from 8 months to 5 years in patients who have discontinued gold. The mean total cumulative dose of gold over 22 years in all patients was 4 g.

CASE REPORTS

Patient 3: FS with recurrent infections. A 66-year-old woman was referred to the gold clinic in 1989 with RA and recent diagnosis of FS. Symptoms developed in 1964 in metatarsophalangeal joints and subsequently knees, elbows, and small joints of the hands, causing typical rheumatoid deformities. Extraarticular features included Raynaud's phenomena and sicca symptoms. Treatment had consisted of nonsteroidal antiinflammatory medications and intermittent prednisone. She had never taken DMARD. Over the course of 2 years before the referral, she had 2 episodes of pneumonia requiring hospitalization, one episode of cellulitis, 2 urinary tract infections, and persistent pharyngitis. She was

Table 1. Patients and disease characteristics.

Patient	Age, yrs	Sex	RF	Splenomegaly*	Infections	BMB	Medications at Time of FS Diagnosis
1	67	F	+	+	—		Gold
2	58	F	+	—	—	+	Chronic prednisone therapy, MTX
3	66	F	+	+	Recurrent infections (see text)		Prednisone, NSAID
4	56	F	+	—	—	+	Prednisone
5	67	F	+	+	—	+	NSAID, gold
6	74	F	NA	—	—		None
7	50	F	+	+	—		None
8	42	F	+	—	—		Minocycline, plaquenil
9	55	M	+	+	—		Prednisone, (MTX DC prior to FS due to adherence problem or lack of efficacy), gold, plaquenil
10	58	F	+	—	—	+	Penicillamine, gold
11	63	F	+	+	—	—	Prednisone, MTX, plaquenil
12	73	F	+	—	—		Prior use of MTX; gold, sulfasalazine, plaquenil
13	34	F	+	+	—		Prednisone, NSAID

* Abdominal ultrasound was done on Patients 1, 2, 4, 7, 8, 9, 11, 12, and 13. For the rest, physical examination was used to detect splenomegaly. BMB: bone marrow biopsy; findings were normal cellularity with maturation arrest. NA: not available, MTX: methotrexate, DC: discontinued.

Table 2. Summary of gold treatment. Patients 2 and 11 developed FS while taking MTX. Patients 5 and 13: gold discontinued because of thrombocytopenia and gold dermatitis while FS was active. Patients 8 and 12 did not normalize WBC: however they are still on gold and FS controlled. Patient 10 was switched to cyclosporine due to scleritis. Patients 6 and 7 were discharged from clinic to be followed by their family physicians. Patients 4 and 11: gold was discontinued following complete normalization of WBC due to rash and low persistent proteinuria.

Patient	Duration of Treatment	WBC at Presentation of FS ($\times 10^3$ per µl)	WBC Count in Response to Treatment	Time to Response, mo	Total Dose	Side Effects
1	02/1988–present	3.7 (lowest = 2.3)	4.1	32	13,700	Proteinuria
2	12/2001–present	1.8	4.1	3	1560	None
3	09/1989–present	2.1 (lowest = 1.9)	4.2	8	7650	Proteinuria, rash
4	11/1984–02/1987	2.2 (lowest = 1.8)	4.4	12	4956	Rash
5	10/1979–08/1982	3.7 (lowest = 2.6)	2.6	NN	3210	Thrombocytopenia
6	10/1989–06/1990	2.1	4.1	4	860	None
7	04/1989–05/1986	3.3 (lowest = 2.6)	4.7	6	1490	None
8	09/2000–present	3.1	3.7	NN	930	Rash
9	10/2000–present	2.8	4	2	2192	Rash
10	09/1981–05/1985	3.4	4.5	19	1155	Rash
11	08/1995–01/1998	3.4 (lowest = 1.3)	4.7	3	10,010	Proteinuria
12	05/1999–present	3.6 (lowest = 2.8)	3.5	NN	3150	Rash
13	04/1990–12/1990	2.9	3.1	NN	770	Rash

NN: not normalized.

found to have splenomegaly on physical examination. Laboratory results included WBC count 2.1 × 10^3/µl, polymorphonuclears 0.3 × 10^3 (3.0–6.0), hemoglobin 10.6 g/dl, mean corpuscular volume 77 µm^3, platelets 279 × 10^3/µl, strongly positive RF, erythrocyte sedimentation rate (ESR) 76 mm/h, 0.3 g/l proteinuria, creatinine 74 µmol/l. A diagnosis of FS was made and gold therapy was initiated in September 1989. WBC count dropped further to 1.4 × 10^3/µl in October 1989 after a cumulative dose of 235 mg. Gold was held back. A week later her WBC count increased to 1.9 × 10^3/µl and gold 25 mg was restarted on a weekly basis. In December 1989, ESR was 34 mm/h. In January 1990, laboratory tests included hemoglobin 12 g/dl and WBC count 2.7 × 10^3/µl. In March 1990, significant improvement in

energy level, morning stiffness, and sicca symptoms was reported. She had a painful ulcer affecting the lateral aspect of the left third toe that improved with a topical antibiotic and steroid ointment. WBC count then was 4.5 × 10^3/µl (48% neutrophils) and it has remained in the normal range to the present time. There have been no further infections. Between 1990 and 2003, there were 2 episodes of mild proteinuria attributed to gold and recurrent gold dermatitis that required temporary discontinuation of gold and dose titration. The lowest dose of gold was 2 mg/week and the average maintenance dose was 50 mg every second week.

Patient 2: FS developing while taking MTX. A 58-year-old woman was referred to the gold clinic in August 2001. She presented in December 1999, with RA since 1995. Symptoms initially started in her left shoulder. Subsequently, the neck, proximal interphalangeal joints, metacarpophalangeal joints, wrists, and left knee joint had been affected. RF was positive. She had long-standing psoriasis. Over 6 years, her disease had been slowly progressive. She was treated with chronic prednisone therapy complicated by osteoporosis. Sulfasalazine was discontinued after 2 years due to rash. MTX 10 mg orally, flurbiprofen 100 mg tid, and folate 5 mg daily were started in December 1999. WBC count at that time was 4.5 × 10^3/µl, hemoglobin 13.5 g/dl, platelets 262 × 10^3/µl, and ESR 11 mm/h. Six weeks later her disease was still active clinically: MTX dose was increased gradually to 20 mg by subcutaneous injection instead of orally. Hydroxychloroquine 400 mg daily was added in April 2000. WBC count started to decrease beginning July 2001, when her count was 3.3 × 10^3/µl. She remained off MTX temporarily, but despite this WBC count continued to drop and reached 1.6 × 10^3/µl in November 2001 (Figure 1). Ultrasound of the abdomen was done in August 2001, and the result was normal. Bone marrow biopsy in November 2001 following a hematology consultation showed normal cellularity with maturation arrest. This was felt to be consistent with FS. In December 2001 gold was started. The initial doses of gold were as usual 10, 25, and 50 mg IM weekly injection. Within 3 months, WBC count had normalized at 4.1 × 10^3/µl, hemoglobin 13.7 g/dl, platelets 231 × 10^3/µl, and ESR 11 mm/h. In September 2002, MTX 10 mg IM injection was added to gold therapy due to a flare in arthritis and psoriasis; FS was in remission, with WBC count 4.3 × 10^3/µl. Currently, her disease is under good control, on combination gold 50 mg IM per week and MTX 10 mg po per week. The total cumulative dose of gold is 2760 mg.

DISCUSSION

The gold clinic at the Mary Pack Arthritis Centre normally admits and discharges about 50 patients per year and serves for routine injection care and monitoring about 250 patients. Between 1979 and 2003 it is estimated that about 1200 may have attended. Thus FS may occur in 1%. The demographic features of FS presented here are consistent with those previously reported[4,6,17]. In contrast to RA, FS is genetically homogeneous with respect to the best characterized genetic determinant, HLA-DR4. Lanchbury, *et al*[18] reported over 90% of patients with FS were DR4-positive, compared with 60–70% of RA patients and roughly 30% of Caucasian controls. In addition, Wordsworth, *et al*[19] found an excess of DR4 homozygotes, particularly *0401/*0404 compound heterozygotes, giving a high relative risk for disease development. It is primarily the *0401 allele that is associated with progression to FS or severe RA. Coakley, *et al*[20] investigated the role of HLA class I in susceptibility to FS and large granular lymphocyte (LGL) syndrome. They concluded the extended haplotypes reported in a number of studies for FS and RA (summarized as: HLA*02; Cw*0501; B*44; TNFb5; TNFa6; TNFd4; C4A*3; C4BQ*0; DRB1*0401; DQB1*0301) are likely to be attributable to strong primary association with HLA-DRB1*0401, rather than to epistatic interaction between these loci. Although many mechanisms of white blood cell destruction have been promoted, the pathogenesis of neutropenia in FS remains incompletely understood. Starkebaum, *et al*[21] found that both soluble immune complexes and antibodies reactive with polymor-

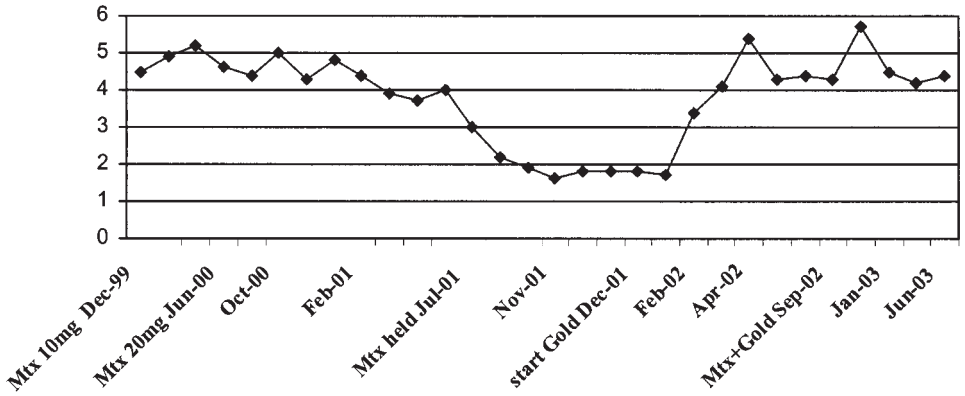

Figure 1. WBC counts in Patient 2, who developed FS while receiving MTX.

phonuclear (PMN) leukocytes contributed to the elevated serum levels of IgG PMN-binding activity seen in sera from some patients with FS. Dancey, *et al*[22] evaluated neutrophil marrow cellularity in 14 neutropenic patients with RA from measurements of neutrophil-normoblast ratios in marrow biopsies and ferrokinetic estimates of marrow normoblasts. The pattern in 2 patients with FS was consistent with a physiological response to neutrophil destruction. The other 12 patients had neutrophil marrow abnormalities. Seven patients with FS and 4 patients without splenomegaly had absolute or relative hypoplasia of neutrophil marrow or low maturation ratios. One patient with a normal spleen size had an increased number of marrow segmented cells, yet failed to mobilize cells normally in response to dialysis coil activation of C3. Abnormalities of neutrophil marrow may contribute to neutropenia in RA, irrespective of the presence of splenomegaly. Meliconi, *et al*[23] examined the production in patients with FS of 5 cytokines involved in the maturation and activation of PMN cells: interleukin 1ß (IL-1ß), tumor necrosis factor (TNF)-α, IL-8, granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage-colony stimulating factor. Serum IL-8 concentrations were elevated in patients with FS and RA compared to controls, but there was a weak inverse correlation between neutropenia and serum IL-8 concentrations. They concluded that neutropenia of FS cannot be explained by changes in peripheral blood cytokine production. However, there might be a role for IL-8. Coakley, *et al*[24] found no association between FS or RA and recently identified IL-10 promoter polymorphisms. Coakley, *et al* in another report[25] found that expansion of CD8+, CD57+ T cells in the bone marrow may be responsible for neutropenia by suppressing neutrophil precursors. Hellmich, *et al*[26] found IgG antibodies against G-CSF detected by ELISA in 11 of the 15 FS patients (73%). In contrast, no patient in the RA control group had either IgG or IgM antibodies against G-CSF. Bone marrow abnormalities include most commonly a maturation arrest of the granulocyte cell line, hypoplasia, and rarely a lymphocytic infiltration; overall cellularity is either normal or reveals myeloid hyperplasia[4]. Neutrophil phagocytosis in the bone marrow may be another mechanism of leukopenia in FS[27].

Autoantibody levels are typically more prominent in FS than in RA. It has been reported that 83% of 24 patients with FS had antihistone antibodies, often at high concentrations[28]. Antineutrophil cytoplasmic antibodies (ANCA), detected by indirect immunofluorescence on ethanol-fixed neutrophils, were found in 77% of 30 patients with FS and in 36% of 50 RA patients. Antibodies against lactoferrin occurred more frequently in FS patients (50%) than in RA patients (4%)[29].

According to Rosenstein, *et al*[1] the degree of splenomegaly bears no relationship to the degree of neutropenia, placing in question the pathogenetic role of the spleen in the neutropenia of FS and whether splenomegaly should be a necessary diagnostic criterion for FS. The presence and the degree of splenomegaly is of minor importance for the risk of infections, since RA patients with neutropenia but without splenomegaly have the same clinical course in terms of extraarticular manifestations and infections as patients with the complete triad[30]. We did not include splenomegaly as an essential criterion for FS. Previous investigators have not included splenomegaly as an essential criterion for FS diagnosis[4,20,25]. Splenectomy is not protective from developing recurrent infections[1,17,31].

Breedveld, *et al*[32] found the incidence of infections increased significantly only with absolute neutrophil counts < 100/µl. At levels > 100/µl no association was found between absolute neutrophil counts and the incidence of infections. Other factors found to be associated with an increased incidence of infections were severe disability, skin ulcers, glucocorticosteroid dose, monocyte counts, hypocomplementemia, and high levels of circulating immune complexes. The activity of the RA, ESR, hemoglobin concentrations, and lymphocyte counts were not associated with increased incidence of infections. Hellmich, *et al*[33] recruited 13 consecutive patients with FS and 10 consecutive patients with systemic lupus erythematosus who had an absolute neutrophil count < 1500/µl for at least 3 months. The absolute neutrophil count was similar in neutropenic patients who did and did not have infection. Therefore, the absolute neutrophil count is an insensitive and nonspecific marker for susceptibility to infection in patients with mild to moderate neutropenia due to rheumatic disease. The interesting finding was the median concentration of soluble Fcγ receptor III was significantly lower among patients who developed infections, whereas the median concentration of G-CSF was significantly higher compared with patients without infections. Soluble Fcγ receptor III is the soluble form of a membrane receptor expressed mainly by mature neutrophils[34]. Serum concentrations correlate positively with neutrophil production and turnover[35]. These are better indicators of the risk of infection than the neutrophil count[33]. Sibley, *et al* also found no correlation between WBC count or PMN counts and the risk of infection[17]. Given these findings, when to consider treatment of FS remains a valid question.

The largest series of patients with FS was reported by Dillon, *et al* in 1986[4]. Twenty patients were treated with parenteral gold. Splenomegaly was not required for inclusion. The following criteria were used for response to therapy. Complete response was defined as: increase in WBC count to ≥ 3×10^3/µl and granulocyte count to ≥ 2×10^3/µl plus 2 of the following: (1) reduced infection rate of at least 50%; (2) decreased incidence of cutaneous ulcers of at least 50%; (3) reduced incidence of febrile episodes by at least 75%. Partial response was defined as: increase in WBC count to ≥ 2×10^3/µl or granulocyte count to between 1×10^3 and 2

× 10^3/µl plus 2 of the following: (1) reduced infection rate of at least 25%; (2) decreased incidence of cutaneous ulcers of at least 25%; (3) reduced incidence of febrile episodes by at least 25%. Based on these criteria, 60% of Dillon's series experienced a complete response with gold therapy, 20% experienced a partial response, and 4 patients had no response to treatment. With regard to the 4 patients who had no response to parenteral gold therapy: one had received gold for only 2 months, one had ongoing infection and leukopenia and eventually died, and 2 showed no improvement in leukocyte counts, although there was a significant symptomatologic improvement in one. Bellelli, *et al* reported treating 5 FS patients with auranofin 6 mg/day[5]. All 5 had improvement in arthritis symptoms and normalization of the WBC count.

There have been no randomized controlled trials with any of the DMARD to address their efficacy of use in FS. Low dose MTX in several case reports was effective in improving symptoms and increasing WBC count[6-8]. Wassenberg, *et al* describe 7 patients with FS who received MTX at a mean dose of 13 mg/week[6]. The mean granulocyte count showed an insignificant rise after one month, but increased 2-fold after a year. Leflunomide use was effective in one patient with profound neutropenia who did not respond to hydroxychloroquine, parenteral gold, MTX, or etanercept[13]. Although the anti-TNF agents have been in use for several years, there are no reports of their use in FS. The coexistence of FS excluded patients from most anti-TNF trials because of concerns about increased risk of infectious complications.

Gold treatment results in reduction of rheumatoid factors and circulating immune complexes. This may explain the beneficial effect of gold in FS. No other mechanisms have been proposed or studied. Response of WBC count is similar to response of joint inflammation in the sense that improvement is normally seen by 12–24 weeks, but maximum benefit may take a year or longer.

During the 24 years included in this chart review, we identified only one patient (Patient 3) with serious infectious complications of FS. This patient received no DMARD for 23 years from the time of diagnosis of RA to the time she first experienced infectious complications. In 12 of 13 patients, FS was asymptomatic. In this respect, our experience is consistent with the prevailing impression that FS in the majority is a benign condition. Nevertheless, FS in the clinic was considered a medical concern when WBC counts fell and remained below the normal range and when low WBC counts began to interfere with treatment decisions.

Because our chart review does not include any comparison group, it is not possible to determine the reasons that serious complications are rarely seen. It is possible that earlier and better DMARD therapies have altered the course of extraarticular disease as well as the arthritis. In previous studies, for example, the mean duration of the neutropenia at the time of entry to the study was 4–5 years[32]. In contrast, the diagnosis of FS in our patients was established within a few months of the onset of leukopenia. The new concept in the management of RA over the last decade has greatly influenced the natural history of this disease. Early and combination use of DMARD has affected the clinical outcomes in RA patients. In a cohort of 609 RA patients, the use of DMARD was not associated with increased risk of infection in multivariate analyses, after adjustment for demographic characteristics, comorbidities, and disease related variables[36].

The case reports above illustrate the approach to diagnosis of FS. Potentially myelotoxic medications are discontinued for 1–3 months of observation. Chart review, history, physical examination, and laboratory evaluation should rule out chronic viral illness and cyclic neutropenia. Abdominal ultrasound is performed to measure spleen size. If splenomegaly is not found, normally the patient is referred for bone marrow biopsy. In 3 of 12 patients the diagnosis of FS was made clinically. These patients had normal spleen size, and bone marrow biopsy was not done. In each of these patients, potentially myelotoxic drugs were discontinued. Improvement in WBC counts did not occur. Chart review and observation of these patients ruled out other diagnoses such as cyclic neutropenia or viral infections. Followup of a mean of 38 months has not resulted in clues to any infiltrative or myelodysplastic process. Nevertheless, we cannot exclude the possibility that in these 3 patients the cause of neutropenia is actually not FS.

Management of FS with DMARD can be difficult. In our clinic we have considered a 30% reduction of the WBC count from baseline to be a cause for concern. This degree of reduction normally mandates a temporary withdrawal of gold or other potentially myelotoxic DMARD until the laboratory results show stability. If there is no trend to worsening, DMARD may be cautiously reintroduced with careful monitoring.

Previous studies used a combination of laboratory and clinical criteria to measure improvement in FS[4]. Because FS was asymptomatic in 12 of 13 cases in our study, our evaluation of outcome relies entirely on normalization of WBC count.

This chart review allows us to evaluate the presentation and course of FS in the current era of RA management that normally employs early DMARD therapies. FS still occurs in about 1% of patients seen in our gold clinic. Notably, only one of our patients experienced infectious complications. Vasculitis did not occur. Our review confirms the impression that serious complications of FS are now rare.

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