

## **RHEUMATOID ARTHRITIS**

### **R1 A Systematic Review of Infection Risks Among Rheumatoid Arthritis Patients Receiving Biologic Agents**

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**INTRODUCTION:** Infection has been identified in studies as one of the leading causes of mortality among patients with rheumatoid arthritis (RA). Several RA cohorts have confirmed this increased risk of infection with risks ranging from 5.3 to 14.9. The introduction of biologic response modifiers, more commonly known as biologic agents, in the treatment of RA has stirred interest on this group of drugs' impact on RA co-morbidities, particularly infections.

**OBJECTIVE:** To systematically review the risk of developing infections among RA patients enrolled in randomized controlled trials (RCT) involving biologic therapies.

**METHODS:** A MEDLINE search (1999 to October 2005) was done using the terms rheumatoid arthritis, biologic agents, and the specific names of the biologic agents. This was supplemented by citation tracking of bibliographies and conference proceedings and searching the Cochrane Database for existing meta-analyses and systematic reviews.

**RESULTS:** Twenty-three (23) studies were retrieved following using the search strategy outlined above. However, only 18 studies were included in the analysis as the incidence rates of infections could not be extracted from the published safety data in the excluded studies. All included trials were independently assessed to be of fair quality. The included trials randomized a total of 11,323 patients to receive either a biologic agent or a placebo.

The incidence of infection among rheumatoid arthritis patients was not increased by the administration of biologic agents [Relative risk 1.01, 95% CI (0.96, 1.07)]. However, serious infections, which required intravenous antibiotic administration or necessitated hospital admission, were significantly higher in the group receiving biologic agents [Relative risk 1.35, 95% CI (1.04, 1.75)]. This risk was higher in the groups receiving Anakinra, an IL-1 receptor antagonist, and Infliximab, a TNF- $\alpha$  inhibitor.

**CONCLUSION:** Aside from the potential to alter disease course among patients with RA, biologic agents predisposes patients to developing serious infections. Further studies of are needed to determine if this treatment associated risk is higher than that observed with traditional DMARDs.

### **R2 Rituximab for Rheumatoid Arthritis with Overlap Syndrome in a Filipino previously treated for CD20+ Hodgkins Lymphoma: A Case Report**

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**BACKGROUND:** There is a close association between autoimmune diseases and lymphoproliferative disorders. Rituximab, an anti-CD20 monoclonal antibody has been widely used in the treatment of Non-Hodgkins lymphoma, and recently been found effective for rheumatoid arthritis (RA) and other autoimmune diseases. We report an unusual case of active RA – also seropositive for systemic lupus erythematosus (SLE) and autoimmune thyroid and liver disease – developing in a patient previously treated for CD20+ Hodgkins lymphoma, who responded to rituximab therapy.

**CASE REPORT:** A 59 year old Filipino female was diagnosed 8 years ago with Hodgkin's lymphoma (positive for B cell markers CD15, CD20, CD30 and CD45), successfully managed with standard chemo-

and radio-therapy. Over the subsequent years, she experienced intermittent joint pains with occasional swelling, and sequentially developed manifestations of organ-specific (thyroid and liver) autoimmune diseases. She presented to the Rheumatology Clinic in 2007 with persistent progressive polyarthritis of 3 months duration, accompanied by morning stiffness. Hemoglobin was 115g/L, white blood cell count  $4.53 \times 10^9/L$  (neutrophils 54%, lymphocytes 32%), and platelets  $285 \times 10^9/L$ ; urinalysis was normal. Erythrocyte sedimentation rate (ESR) was 89 mm/hr, and C-reactive protein (CRP) 96. Alanine (ALT) and aspartate (AST) transferases were 224 IU/L and 177 IU/L respectively. Serum creatinine, creatine kinase, complement (C3), and hepatitis B and C serology were normal/negative. Serum LDH was slightly elevated at 758 U/L (NV 313-618), thyroid functions were normal. Rheumatoid factor (RF) and anti-CCP were strongly positive at 2560 IU/ml and 1100 U/ml, respectively. Anti-nuclear antibody (ANA) was positive up to 1:5120 titer (speckled pattern), anti-dsDNA weakly positive at 262.18 (NV up to 200). She also had antibodies to histone (3.24), thyroglobulin (228 IU/ml, NV <40) and smooth muscle. Antibodies to RNP, SSA (Ro), SSB (La), Scl 70, thyroid peroxidase and mitochondria were negative. Chest radiograph showed subsegmental atelectasis on the left lung field; hand radiographs showed joint space narrowing on some proximal interphalangeal joints with juxta-articular osteopenia. She was started on oral steroids which were rapidly tapered from 40 to 5 mg/day. Since the liver disease contraindicated use of methotrexate or leflunomide, she opted for rituximab therapy – which was administered as 1 g infusion for 2 doses, 2 weeks apart. She tolerated the therapy well, and reported dramatic clinical improvement, which was sustained throughout the subsequent months.

**CONCLUSION:** This case illustrates the strong associations between autoimmunity and lymphoproliferative disorders. It also emphasizes the role of B cells as a common and dominant pathway in the pathomechanisms of these diseases, and reinforces the mechanism of action of rituximab as an effective B-cell targeted therapy.

### **R3 Prevalence of Hearing Loss Among Patients with Rheumatoid Arthritis: A Preliminary Report**

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**BACKGROUND:** Rheumatoid arthritis has been linked to hearing loss, however, conflicting data regarding this association exist.

**Objective:** This study attempts to determine the prevalence of hearing loss among rheumatoid arthritis (RA) patients and evaluate possible predisposing factors that may contribute to such link.

**RESULTS:** Twenty (20) female RA patients were evaluated for hearing using pure tone audiometry (PTA) at different sound frequencies and tympanometry. The status of rheumatoid arthritis was assessed based on joint counts, ESR, patient global assessment and collectively computed as disease activity score (DAS-28). Other pertinent clinical data such as rheumatoid factor (RF) positivity, duration of illness, initial joint counts, time period prior to initiation of DMARDs, and drug history were also obtained.

Results showed 7 out of 20 (35%) patients manifested hearing loss with sensorineural hearing loss predominating. These appear to be unrelated to disease activity, duration and medications. Final conclusions will be made once data collection is more complete.

### **R4 Anti-cyclic Citrullinated Peptide Antibody Assay in the Diagnosis of Rheumatoid Arthritis among Filipino Patients**

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**OBJECTIVE:** To determine the diagnostic accuracy of anti-CCP among Filipino patients with rheumatoid arthritis.

**RESEARCH DESIGN:** This is a retrospective, cross sectional study all Filipino patients who were tested for both anti-CCP antibodies and Rheumatoid factor from January 2005 – July 2008 at St. Luke’s Medical Center.

**STUDY POPULATION:** The targeted study population consists of all Filipino patients between the ages of 29 – 78 diagnosed with RA according to the American College of Rheumatology criteria (Table I) and all patients with non-RA pathologies (connective tissue diseases, other rheumatoid diseases, viral infections, autoimmune thyroid diseases, and healthy subjects) who were tested for both anti-CCP antibodies and Rheumatoid factor at St. Luke’s Medical Center from January 2005 – July 2008. We will exclude from this study all patients who underwent anti-CCP assay and RF determination at different occasions, patients who underwent only anti-CCP assay and patients who underwent RF determination alone.

**RESEARCH INSTRUMENT:** Written and informed consent for chart review will be obtained from the attending physicians of the study population. Data collection will be done by an independent committee. A separate committee will decide whether included patients have rheumatoid arthritis or not based on chart review and interview of the attending physicians and patients. A separate statistician will analyze the results of this study.

**SAMPLE SIZE CALCULATION:** The sample size was computed based on the following formula for analytic study comparing two frequencies from different population at 95% confidence interval:  $n = (K^2 pq)/d^2$  where n is the sample size, K is the reliability coefficient based on the level of confidence, p is the average of the estimates of the frequencies of the event in the two populations, q is 1-p, and d is the minimum difference between the frequencies to be detected. The computed sample size is 135 patients.

**STATISTICAL ANALYSIS:** Demographic characteristics of all patients will be tabulated as mean  $\pm$  SD for quantitative data. The diagnostic accuracy of anti-CCP assay and rheumatoid factor will be presented as sensitivity, specificity, positive and negative predictive values, and likelihood ratio.

## **R5 Health-related Quality of Life and Functional Status of Filipino Patients with Rheumatoid Arthritis**

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**13<sup>th</sup> PRA Annual Convention. Westin Hotel, Manila. Jan 2006**

APLAR Journal of Rheumatology 2006;9Suppl:A173

**OBJECTIVE:** This study aims to establish the correlation between the domains of functional ability and some characteristics of RA patients including disease duration.

**STUDY DESIGN:** Cross-sectional descriptive study

**SETTING:** Inpatient and outpatient services of Section of Rheumatology, Clinical Immunology, and Osteoporosis of the University of Santo Tomas Hospital between December 2004 to October 2005

**PATIENTS/PARTICIPANTS:** Adult males and females with rheumatoid arthritis confirmed based on American College of Rheumatology (ACR) criteria

**MAIN OUTCOME MEASURES:** Disability was measured using the Health Assessment Questionnaire (HAQ) Disability Index. Pain and global health status were measured by the HAQ Visual Analog Scale and HAQ Global health index.

**RESULTS:** A total of 56 patients were included in the study divided into 51 females (91%) and 5 males (9%). Mean age is 46 years old. The mean duration of RA is 45.98 months. Average BMI is 23.6 kg/m<sup>2</sup>. Results of mean outcome measures are: disability index =  $1.1 \pm 0.81$ , pain =  $1.26 \pm 0.86$ , and global health =  $1.33 \pm 0.72$ . Most patients belong to class IV functional classification. Pain is associated significantly with functional classification ( $p=0.000$ ) and disability index ( $p=0.000$ ). There is a statistically significant association between disability index and patient’s global health ( $p=0.026$ ). Duration of disease is significantly correlated with disability index ( $p = 0.018$ ) and pain ( $p=0.046$ ). There is no statistically significant association between functional classification and patient’s global health ( $p=0.070$ ) and pain and the global health ( $p=0.078$ ).

**CONCLUSION:** HRQOL is reduced in Filipino patients with rheumatoid arthritis. Most have moderate to severe disability, moderate pain, and average global health scale. These HRQOL measures should be determined since they are important measures that help assess and manage RA patients.

**Research Grant:** Rheumatology Educational Trust Foundation, Inc.

## **R6 Risk Factors for Osteoporosis in Filipinos with Rheumatoid Arthritis**

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1. **Poster Presentation. 12<sup>th</sup> APLAR Congress Kuala Lumpur, Malaysia, August 2006.**
2. **APLAR Journal of Rheumatology 2006; 9(suppl.1 P281): A137**
3. **Poster Presentation. 13<sup>th</sup> PRA Annual Convention. Manila, Jan 2007.**

**OBJECTIVE:** This study aims to describe the risk factors for osteoporosis in a cohort of Filipino patients with rheumatoid arthritis (RA).

**DESIGN:** Retrospective, descriptive study

**SETTING:** Joint and Bone Center of the University of Santo Tomas Hospital in Manila, Philippines

**PARTICIPANTS:** Patients with rheumatoid arthritis (RA) who were referred for bone mineral densitometry (BMD) at the Joint and Bone Center of the University of Santo Tomas Hospital in Manila, Philippines, from 2002 to 2005.

**METHODS:** Demographic and clinical data were obtained from patients with rheumatoid arthritis (RA) who were referred for bone mineral densitometry (BMD) at the Joint and Bone Center of the University of Santo Tomas Hospital in Manila, Philippines, from 2002 to 2005. Lumbar spine (LS), femoral neck (FN) and ultradistal forearm (UDFA) BMDs were measured using Lunar DPX-IQ. The variables evaluated were age at BMD test, duration of the RA disease, height, weight, body mass index (BMI), years since menopause, use of cigarettes, coffee, calcium intake, physical exercise, intake of steroid, methotrexate, and hormone replacement (HRT). Only the initial BMD results were considered for those who had serial BMD measurements. The BMD and clinical data were statistically analyzed using comparison of means and linear regression analysis.

**RESULTS:** A total of 128 patients diagnosed with RA underwent BMD within the study period. There were 121 females and 7 males, with a mean age of  $66 \pm 7$  SD, a mean RA disease duration of 7 years  $\pm$  8 SD, and a mean of  $14 \pm 10$  SD years since menopause. Using linear regression analysis, there was a positive correlation between BMD and BMI, and a negative correlation between age, years since menopause with BMD, which were all statistically significant,  $p < 0.05$ . There was some association between RA disease duration with BMD, but this was not statistically significant. There was no significant effect of smoking, coffee drinking, exercise, calcium intake, use of steroid, methotrexate and HRT on the BMD.

**CONCLUSION:** In our cohort of Filipino patients with rheumatoid arthritis, the risk factors for low BMD measurements included low BMI, older age and longer years since menopause. These observations suggest that even among these patients with chronic inflammatory disease, the usual risk factors for involutional osteoporosis are applicable, and must be recognized and appropriately addressed.

**Research Grant:** None

## **R7 Assessment of Physicians' Adherence to Practice Guidelines for Rheumatoid Arthritis**

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1. **2<sup>nd</sup> Place Department of Medicine –UP-PGH Annual Research Forum. 1999**
2. **1<sup>st</sup> Place, Poster Presentation. 30<sup>th</sup> PCP Annual Convention**
3. **Phil J of Internal Medicine. 40: 144-148. May-June 2002**

**OBJECTIVE:** This paper aims to assess physicians' conformity to diagnosis and management guidelines for rheumatoid arthritis set by the American College of Rheumatology (ACR) 1996 Ad Hoc Committee.

**DESIGN:** Descriptive study, case record review

**SUBJECTS:** Adult patients who fulfilled the 1987 ACR criteria for the diagnosis of rheumatoid arthritis.

**SETTING:** UP-Philippine General Hospital (UP-PGH), Rheumatology Clinic

**METHOD:** We reviewed charts of adult rheumatoid arthritis (RA) patients diagnosed at UP-PGH, based on the 1987 ACR criteria, seen between January 1998 to May 2000. Quality of care based on the standards set by the ACR in 1996 was assessed. Data collection forms were drafted based on the practice guidelines on diagnosis, treatment, and follow up. Compliance to the practice guidelines was then measured by determining the frequency by which the criteria were adhered to.

**RESULTS:** Fifty-six patients were included in the study. The standard of good quality was set at 70% adherence. Performance rates were above our set standard with regard to the following measures: evaluation of degree of joint pain and morning stiffness; documentation of inflamed joints and mechanical joint function; baseline evaluation of complete blood count (CBC), rheumatoid factor (RF), erythrocyte sedimentation rate/c-reactive proteins (ESR/CRP), aspartate/alanine aminotransferase (AST/ALT), and platelet count; initial radiographs; initial determination of CBC, and AST/ALT among patients on non-steroidal anti-inflammatory drugs (NSAIDs); blood pressure monitoring among patients on steroids; ophthalmologic examination among patients on anti-malarials; initial determination of CBC, AST/ALT, creatinine, and chest radiographs among patients on methotrexate; and reassessment of degree of joint pain, morning stiffness, inflamed joints, mechanical joint problems, and periodic ESR/CRP determination. Performance rate was below our set standard of 70% for evaluating fatigue, limitation of function, extra-articular manifestation; baseline determination of creatinine, urinalysis, electrolytes and fecalysis; initial creatinine among patients on NSAIDs; initial glucose and cholesterol among patients on steroids; initial alkaline phosphatase, albumin, and chest radiographs among patients on methotrexate; rehabilitation; and reassessment of fatigue, outcome measures, and periodic radiographs.

**CONCLUSION:** Based on practice guidelines, there was good adherence to some measures of clinical evaluation but there were also deficiencies in other areas, specifically functional evaluation. Several aspects of care need to be improved to deliver high quality care.

## **R8 A Review of Adverse Drug Reactions among Rheumatoid Arthritis Patients on Combination Drug Therapy at the Philippine General Hospital Arthritis Clinic**

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**Phil J of Internal Medicine Nov-Dec 2000. 38(6): 304-310.**

**OBJECTIVES:** 1) To state the various drug therapies given to rheumatoid arthritis (RA) patients at the arthritis clinic of the Philippine General Hospital (PGH) 2) To describe the different adverse drug reactions (ADR) resulting from combination drug treatment among these patients 3) To state the outcome of the different ADRs 4) To evaluate the association of some patient and disease characteristics with the development of ADR.

**METHODS:** Review of the hospital charts of all RA patients at the UP PGH who had at least two clinic visits during the period of 1994 to 1997. The following information were collected: demographic characteristics, list of medications, medical illness, duration of RA, ADR and its outcome. The association between the occurrence of ADR and age, sex, disease duration, and duration of drug treatment were determined using chi-square and t-test.

**RESULTS:** There were seventy patients included in this study with a mean age of  $47.07 \pm 13.38$  years. Ninety one percent of the patients were females. The mean disease duration (from the onset of symptoms up to the last follow-up) is  $68.04 \pm 77.07$  months. Pulmonary tuberculosis (PTB) and hypertension were the most common co-morbid conditions. The most common combination of drugs (31.4%) used for our RA patients was a non-steroidal anti-inflammatory drugs (NSAIDs), steroid, methotrexate and chloroquine. Forty-three percent (42.9%) of patients had adverse reactions: 23.3% had skin manifestations and 16.7%

had hematological effects. When the offending medications were withdrawn or dosages were decreased, 76.7% fully recovered from their ADRs. There was significant association between the occurrence of adverse effects with the mean age of  $\geq 52.27$  years and duration of drug use of  $>24$  months.

**CONCLUSION:** 1) The most common drug combination given to the RA patients at the PGH-arthritis clinic was of NSAIDs, steroid, methotrexate and chloroquine. 2) The most common adverse drug reactions observed were gastrointestinal 3) Most RA patients who experienced adverse effects fully recovered from these reactions. 4) The occurrence of ADR was significantly associated with age and duration of drug use.

### **R9 Clinical Profile of Rheumatoid Arthritis among Filipino Patients seen at the University of the Philippines-Philippine General Hospital**

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**Phil J Internal Medicine Nov-Dec 2000. 38(6): 301-303.**

**OBJECTIVE:** To describe the clinical profile of Rheumatoid Arthritis patients seen at the Arthritis Clinic of the University of the Philippines-Philippine General Hospital (UP-PGH) from 1991-1994.

**METHODS:** This paper reviewed the following data: age at onset, sex distribution, duration of symptoms prior to diagnosis, initial joint involvement as to site and pattern, frequency of each criterion in the American Rheumatoid Association (ARA) criteria for the classification of Rheumatoid Arthritis (RA) presence of extra-articular manifestations, co-morbidity, and laboratory parameters.

**RESULTS:** Majority (96%) of the patients were females and the age group most commonly affected are the hand and the wrist joints were most frequently affected and 62.8% presented with more than one joint involvement even at the onset of disease. All patients had arthritis of more than three joints. Seventy-four percent of patients tested positive for rheumatoid factor. Only a small percentage (26.3%) reported concomitant systemic illness and an even smaller percentage (8.3%) had extraarticular manifestations. All patients had elevated ESR values.

### **R10. Anti-Tumor Necrosis Factor Alpha in the Treatment of Methotrexate Resistant Rheumatoid Arthritis: A Meta-Analysis**

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1. **Future in Rheumatology: from bench to bedside. Abstract Book. APLAR 2004. (P217) p. 126**
2. **Poster Presentation. 11<sup>th</sup> APLAR Convention. Korea, September 2004**

**PURPOSE:** Rheumatoid Arthritis (RA) is a chronic inflammatory disease which causes joint damage and disability. Anti-TNF alpha (Adalimumab, Etanercept & Infliximab) have been shown to provide improvement in signs and symptoms of patients with active RA despite treatment with methotrexate. This study aims to determine the effectiveness of anti-TNF alpha combined with methotrexate vs. methotrexate alone in achieving 20%, 50%, and 70% improvement in disease activity as measured by American College of Rheumatology 1991 (ACR) revised criteria and to determine the incidence of adverse events.

**METHODS:** Studies included for this review are randomized double blind placebo controlled trials involving patients with active RA using anti-TNF alpha combined with methotrexate vs methotrexate alone in achieving improvement of disease activity. PubMed, Cochrane and Embase databases were searched. Critical appraisal was made based on randomization, degree of blinding, intention to treat. Discrepancies were discussed with a third party. Data was analyzed using the Review Manager. Improvement in disease activity based on the ACR 20, 50, and 70 and incidence of adverse outcomes were determined. Results were expressed as Odds ratio, fixed effects model at 95% CI. RBI and NNT were also computed.

**RESULTS:** 788 patients were included in the three trials 608 patients were given anti-TNF alpha with methotrexate while 180 patients were given methotrexate alone. Significant improvement in achieving ACR 20, 50, and 70 were noted in the treatment arm vs. control arm (OR 7.30;P<0.0001;RBI 2% NNT 2; P<0.0001), OR 7.59;p=0.0000;RBI 6; NNT 6, p<0.00001) respectively. The adverse effects for the treatment group compared with the control group were not statistically significant.

**CONCLUSIONS:** Outcomes measured favor the probable beneficial effects of anti tumor necrosis factor alpha combined with methotrexate in the treatment of methotrexate resistant RA. These effects should be weighed against adverse effects when used in the treatment for RA.

**R11 Minocycline in the Treatment of Rheumatoid Arthritis: A Systematic Review**  
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1. *Poster Presentation. APLAR 2000 Congress in Beijing, China. May 2000*
2. *Paper Presentation. 7<sup>th</sup> PRA Annual Convention. Jan 2000*

**R12 Mycosis Fungoides in a 25 Year Old Male with Rheumatoid Arthritis: A Case Report**

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A case of a 25-year old male with rheumatoid arthritis was admitted due to skin lesions, hepatosplenomegaly and anemia. The lesions were purplish to dusky red macules sometimes coalescing into patches located all over the body. Flesh-colored papules and nodules were also noted on the face. Biopsy of skin lesions showed infiltrates of atypical lymphocytes which were seen in the upper and deep dermis. The cells exhibited enlarged hyperchromatic and lobulated nuclei with scant cytoplasm. Some cells within the epidermis showed neoplastic lymphoid lesion and is indicative of mycosis fungoides. The cells were positive for CD3 immunostain and is consistent with a T-cell lymphoproliferative lesion, compatible with Mycosis Fungoides.

**R13 Infectious Arthritis among Filipino Patients with Rheumatoid Arthritis: A Case Series**

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**OBJECTIVE.** To describe the clinical features, contributing factors, and clinical course of infectious arthritis (IA) in a group of Filipino patients with rheumatoid arthritis (RA).

**METHODS.** The medical records of RA patients seen at 2 tertiary hospitals were reviewed. Data on demographics, duration of RA, co-morbidities, immunosuppressive use, clinical presentation, etiologic agents, treatment and outcome were obtained.

**RESULTS.** Infectious arthritis (IA) was recorded in 5 RA patients (1 male) among the 49 RA patients regularly seen at St. Luke's Medical Center and University of Santo Tomas Hospital from 2002 to 2007. The age at IA diagnosis ranged from 18 to 71 years, with a mean RA duration of 4.6 years to the onset of infectious arthritis. All were maintained on methotrexate, and 4 were on steroids; other immunosuppressives included leflunomide and cyclosporine, and one patient had received infliximab. The mean duration of joint symptoms prior to IA diagnosis was 3.2 weeks, was mono-articular in 4 and involvement of both knees in 1 patient. The infectious etiology was bacterial in 3 and tuberculous in 2. All had excellent prognosis after appropriate antibiotics, with surgical debridement performed in 4 patients.

**CONCLUSION.** This case series illustrates the importance of considering a superimposed infectious arthritis among RA patients, particularly those with persistent inflammation in 1 or 2 joints out of proportion to the rest of the other established RA joints. Immunosuppressive drug use and a prosthetic joint (1 patient) were among the contributory factors in this series. Early diagnosis and aggressive management likely led to the favorable outcomes of our patients.