Treatment failure with disease-modifying antirheumatic drugs in rheumatoid arthritis patients

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INTRODUCTION Rheumatoid arthritis (RA) patients taking disease-modifying antirheumatic drugs (DMARDs) may experience treatment failure due to adverse effects or a lack of efficacy/resistance. The purpose of this study was to evaluate the prescription patterns, the incidence and reasons for failure, and the time to treatment failure of DMARDs in RA patients.

METHODS The medical records of patients visiting the Rheumatology Clinic were scrutinised retrospectively in order to extract the relevant data, including demographics, clinical and laboratory investigations and drug usage, for analysis.

RESULTS More than 60% of the 474 eligible patients were started on a combination of DMARDs. Hydroxychloroquine (HCQ) (79.7%) and methotrexate (MTX) (55.6%) were the most common DMARDs prescribed initially. There was a significant difference in survival times among the various treatment groups ($p \leq 0.001$). Adverse effect was the main reason for treatment failure of sulfasalazine (SSZ) (88.9%) and MTX (75%), while addition or substitution DMARDs was more common for those taking HCQ (72.2%). Adverse event was reported as the most significant predictor of treatment failure. The most commonly reported adverse effects were bone marrow suppression and hepatotoxicity.

CONCLUSION A combination of DMARDs was used to initiate therapy in more than 60% of RA patients, with HCQ and MTX being prescribed most frequently. Adverse effects accounted mainly for treatment failures with MTX and SSZ, while lack of efficacy was responsible for major treatment failures with HCQ.

Keywords: discontinuation, disease modifying antirheumatic drugs, rheumatoid arthritis, treatment failure, withdrawal
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INTRODUCTION

Rheumatoid arthritis (RA) is characterised by a chronic fluctuating course, resulting in progressive joint destruction, deformity and disability, despite therapy in most patients. American College of Rheumatology (ACR) guidelines[1] recommend the initiation of disease-modifying antirheumatic drug (DMARD) therapy within three months of diagnosis of RA due to its proven role in controlling disease activity, reducing joint erosions and improving quality of life. However, once remission is achieved with DMARDs, there is no clear guideline for maintenance therapy, although strategies are described in situations requiring drug withdrawal/dose modification due to the occurrence of adverse drug reactions (ADRs), lack of efficacy and development of resistance.[2-5]

Only a limited number of studies[6-10] analysing the survival and failure of DMARDs in RA patients have been conducted in varied populations. Such research is necessary in order to study pharmacogenetic variations in the pattern of RA in different populations[11] as well as the genetic differences in the efficacy and safety of the drugs.[12-16] Keeping in mind the paucity of such data in the Indian population, the present study aimed to retrospectively evaluate the patterns of DMARD prescription and the incidence of, and reasons for, treatment failure with different DMARDs in RA patients in a tertiary care hospital in North India. The secondary objectives were to determine the patterns of DMARD prescription, the average number of DMARDs prescribed to an RA patient (single and multiple agent initiations) and the mean duration of intake of a particular DMARD.

METHODS

For this study, we screened all the medical records of patients who presented to the Rheumatology Clinic of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, for the presence of RA. Male and female patients who fulfilled the ACR criteria for RA were included in the study. Patients who did not return to the clinic after the DMARD therapy was prescribed were considered to be lost to follow-up and their numbers were recorded.

Data extracted included age, gender, duration of arthritis and drug usage. The date of initial prescription of DMARD therapy, along with the date of any subsequent change, was noted down. The types of DMARDs prescribed initially and added/substituted later, along with the reasons, were recorded. Consumption of other drugs, such as steroids and analgesics, was also noted. In addition, the charts were scrutinised for results of glucose-6-phosphate dehydrogenase (G6PD) estimation, eye testing, blood counts and biochemistry, urine examination, pulmonary

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Table I. Characteristics of patients with RA (n = 474).

Characteristic	No. (%)
Mean age ± SD (yrs)	41.72 ± 12.24
Female gender	394 (83.1)
Median duration of RA at first visit; IQR (mths)	36; 12–84
Total no. of DMARDs tried during the course of treatment	
1	159 (33.6)
2	240 (50.6)
3	64 (13.5)
4	1 (0.2)
None	10 (2.1)
Initial DMARDs prescribed	
MTX + HCQ	135 (28.5)
HCQ	117 (24.7)
HCQ + SSZ	62 (13.1)
MTX + HCQ + SSZ	52 (11.0)
MTX	36 (7.6)
MTX + SSZ	33 (7.0)
SSZ	25 (5.3)
MTX + HCQ + LEF	2 (0.4)
HCQ + LEF	2 (0.4)
Concomitant therapy	
NSAIDs	350 (73.8)
Steroids	270 (57.0)
Acetaminophen	246 (52.0)
Amitriptyline	14 (3.0)

SD: standard deviation; RA: rheumatoid arthritis; IQR: interquartile range; DMARDs: disease-modifying antirheumatic drugs; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; NSAIDs: non-steroidal anti-inflammatory drugs

function testing and details of clinical examination, in order to assess for any adverse events.

Treatment failure included sustained disease activity requiring addition/substitution of a second DMARD (due to the lack of efficacy or emergence of resistance) and treatment discontinuation (due to appearance of adverse effects). Sustained disease activity was defined as tender joint count > 1, swollen joint count > 1, patient's global assessment > 1 on a 0–10 scale and C-reactive protein level > 1 mg/dL. The study was conducted after obtaining approval from the institute's Ethics Committee.

Data were presented as number, percentage, mean ± standard deviation (SD), median (interquartile range [IQR]), depending on the nature of the data. The primary analytical methods employed for assessing time to treatment failure were Kaplan–Meier survival curves using Breslow (generalised Wilcoxon) test for comparison among different groups. In addition, Cox proportional hazard models were used to predict time to treatment failure after adjusting for various confounding variables. The median (IQR) durations of intake of various DMARDs were compared using Kruskal Wallis test. A p-value < 0.05 was considered to be significant for all statistical comparisons. All analyses were carried out using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 1,400 medical records were screened, out of which 650 (46.4%) patients with RA were detected. Of these, 176 (27%) were considered to be lost to follow-up, and data on 474 patients (33.8% of screened patients) were available for analysis. The median (IQR) duration of follow-up from the initial prescription of DMARDs reflected in the time charts was 10 (range 5–14) months.

The characteristics of the 474 patients included in the analysis and the prescription patterns of DMARD are presented in Table I. More than 80% of the patients were female. The mean age of the patients was 41 years, with a median duration of disease of 36 months at presentation. DMARDs were prescribed in about 98% of the patients. Most of the patients were treated with one or two DMARDs during the course of their therapy, with an average of 1.8 DMARDs per patient. The most commonly used DMARDs were hydroxychloroquine (HCQ), methotrexate (MTX) and sulfasalazine (SSZ). The most common initially prescribed DMARD in both single and combination patterns was HCQ (370, 79.7%), followed by MTX (258, 55.6%). More than 60% of the patients were put on combination DMARD therapy at the time of treatment initiation. MTX and HCQ was the most common combination used. Few patients were treated with triple DMARD therapy at the first visit. Non-steroidal anti-inflammatory drugs (NSAIDs), steroids and acetaminophen were the most common concomitant therapies prescribed. Two patients exhibited deranged liver function tests at baseline and one was previously treated for interstitial lung disease; hence, MTX was not the DMARD of choice in these patients. SSZ was not used in two patients due to G6PD deficiency. The median (IQR) durations of intake of the three most common DMARDs, prescribed as single or combination therapy and at either treatment initiation or as addition later, were nine (5–12) months, nine (5–14) months and ten (5.75–17) months for MTX, HCQ and SSZ, respectively. No statistically significant difference was observed in the overall duration of intake of the three drugs (Kruskal Wallis test, KW = 4.47; p = 0.11).

The numbers and time to treatment failure for various initially prescribed DMARD therapies and the corresponding survival curves are shown in Table II and Fig. 1. There was a significant difference in survival times between the groups (Breslow [generalised Wilcoxon], chi = 64.357, df = 8, $p \leq 0.001$). Table III shows the type of new DMARDs added subsequently in cases with insufficiently effective initiation therapies. Major additions in therapy were with MTX followed by SSZ. Out of the 272 patients prescribed MTX as single/combination therapy at any time during the course of treatment, 12 (4.4%) experienced ADR-related withdrawals. There were five out of 375 (1.3%) and eight out of 180 (4.4%) such discontinuations with HCQ and SSZ, respectively. Fig. 2 demonstrates the survival estimates for ADR-related treatment discontinuation of the three commonly prescribed DMARDs. Times to treatment failure (mean ± standard error and 95% confidence interval [CI]) due to occurrence of adverse events for MTX, HCQ and SSZ were 87.69 ± 2.51 months (82.76, 92.62), 24.68 ± 0.14 months (24.39,

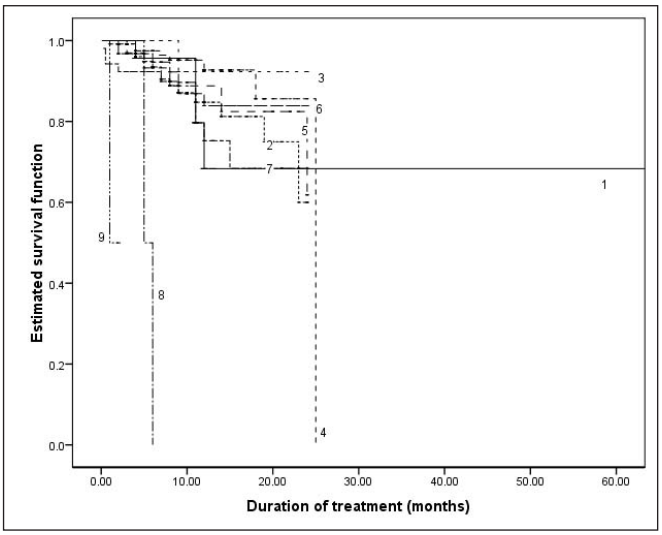

Fig. 1 Kaplan–Meier survival estimates for time to treatment failure due to discontinuation and substitution/addition of other DMARD therapy for various initially prescribed DMARD therapies.
1: MTX; 2: HCQ; 3: SSZ; 4: MTX + HCQ; 5: MTX + SSZ; 6: HCQ + SSZ; 7: MTX + HCQ + SSZ: 8: MTX + HCQ + LEF; 9: HCQ + LEF

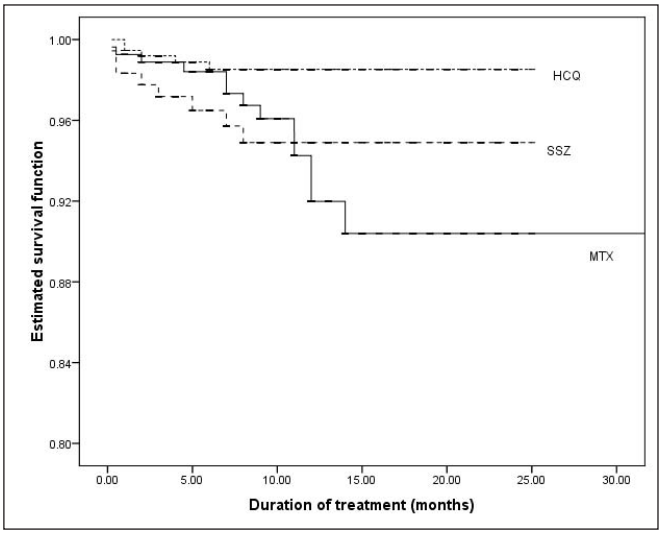

Fig. 2 Kaplan–Meier survival estimates for time to treatment discontinuation due to appearance of adverse drug reactions for patients treated with MTX (methotrexate), HCQ (hydroxychloroquine) and SSZ (sulfasalazine).

24.96) and 23.91 ± 0.37 months (23.18, 24.65), respectively. No significant difference in the three groups of patients taking MTX, HCQ and SSZ was observed in terms of survival times (Breslow [generalised Wilcoxon] test, $\chi^2 = 4.921$, df = 2, p = 0.085). The observed delay in the survival time of MTX could be explained by the fact that the drug was withdrawn in one patient after 96 months of use due to pancytopenia and substituted with SSZ, and a decrease in the mean value was noted after excluding this outlier value from the analysis. Table IV depicts the types of adverse effects reported with various DMARDs.

For all treatment failures with MTX, HCQ and SSZ (single and combination therapies), we calculated the percentage of patients failing treatment due to the two proposed components, i.e. treatment discontinuation and addition/substitution of a second DMARD. It was observed that adverse effect-related therapy discontinuation was the reason for maximum treatment

Table II. Incidence and time to treatment failure of initially prescribed DMARD therapies.

Treatment	Total no. of failures (%)	Time to treatment failure* (mths)
MTX	4 (11.0)	68.88 ± 11.97 (45.43, 92.34)
HCQ	14 (12.0)	20.56 ± 0.84 (18.92, 22.2)
SSZ	1 (4.0)	22.85 ± 1.11 (20.67, 25.02)
MTX + HCQ	8 (6.0)	23.24 ± 0.74 (21.8, 24.69)
MTX + SSZ	5 (15.2)	21.31 ± 1.39 (18.59, 24.03)
HCQ + SSZ	7 (11.3)	21.41 ± 0.91 (19.64, 23.19)
MTX + HCQ + SSZ	10 (19.0)	19.27 ± 1.3 (16.71, 21.82)
MTX + HCQ + LEF	2 (100.0)	5.5 ± 0.5 (4.52, 6.48)
HCQ + LEF	1 (50.0)	1.5 ± 0.35 (0.81, 2.19)

*Data is presented as mean ± SE (95% CI).
DMARD: disease-modifying antirheumatic drug; SE: standard error; CI: confidence interval; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide

Table III. DMARDs added after the failure of initial DMARD therapies.

Initial therapy	Add-on DMARD therapy			
	MTX	HCQ	SSZ	LEF
MTX	-	1	1	-
HCQ	8	-	5	-
SSZ	-	1	-	-
MTX + HCQ	-	-	2	-
MTX + SSZ	-	2	-	1
HCQ + SSZ	4	-	-	1

DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine

Table IV. Adverse effects reported in RA patients taking DMARDs.

Therapy and adverse effects	No. of events
Methotrexate	
Transaminitis	4
Icterus	2
Fall in total leukocyte count	1
Pancytopenia	1
Gastritis	1
Drowsiness	1
Rash	1
Fever	1
Poor compliance	1
Hydroxychloroquine	
Intolerance	2
Eye toxicity	1
Dizziness	1
Tingling in ears	1
Rash	1
Sulfasalazine	
Anaemia	2
Rash	2
Transaminitis	1
Icterus	1
Mucositis	1
Anxiety	1
Headache	1
Intolerance	1

RA: rheumatoid arthritis; DMARDs: disease-modifying antirheumatic drugs

Table V. Cox proportional hazard analyses of predictors of all DMARD treatment failures among RA patients.

Variable	OR	SE	Wald	p-value	95% CI
Side effects (Yes/No)	22.24	0.32	96.15	< 0.05	11.96, 41.34
Age	0.99	0.01	0.09	0.76	0.97, 1.02
Male (Yes/No)	0.49	0.46	2.4	0.12	0.2, 1.21
Disease duration	0.99	0.002	2.34	0.13	0.99, 1.00
Concomitant therapy					
NSAIDs	0.54	0.34	3.1	0.08	0.28, 1.07
Acetaminophen	1.17	0.33	0.24	0.63	0.62, 2.23
Steroids	1.25	0.31	0.52	0.47	0.68, 2.31

RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; OR: odds ratio; SE: standard error; CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs

failure in the SSZ (8/9, 88.9%) and MTX (12/16, 75%) groups. On the other hand, more patients taking HCQ treatment failed due to DMARD addition/substitution (13/18, 72.2%).

Among the 464 RA patients prescribed DMARDs in the study, 56 had experienced treatment failure by the time the data were analysed. We assessed variables, such as age, gender, disease duration at the time of presentation, concomitant therapy and adverse events, as predictors of treatment failure using Cox proportional hazard model (Table V). The significance of the overall model was assessed using log likelihood statistic ($\chi^2 = 80.85$, df = 7, $p < 0.05$). Out of the various independent variables tested, adverse events were reported as the most significant predictor of treatment failure (odds ratio 22.24, 95% CI 11.96, 41.34). During the study period, treatment was discontinued in six (0.01%) patients due to significant improvement in symptoms, with the average period of remission being 8.83 months. Out of these six patients, two each were started on MTX + HCQ and HCQ + SSZ, one on HCQ and one on triple DMARD therapy (MTX, HCQ and leflunomide). Three women conceived while on treatment, leading to treatment withdrawal at 2, 5 and 12 months. The data of these patients were included in the survival analysis.

DISCUSSION

In the present study, time to withdrawal from treatment due to adverse effects and addition/substitution of other DMARD therapies due to inadequate efficacy or emergence of resistance were studied as two separate and integral components of time to treatment failure with DMARDs in RA patients. This is because time to treatment discontinuation does not suffice to explain treatment failure in a condition like RA, where there is a tendency for additional DMARD therapies to be prescribed in the face of insufficient efficacy rather than simply discontinuing treatment. Hence, it is necessary to take into account this additional factor of treatment failure.

The various initially prescribed single and combination therapies differed significantly in incidence and time to treatment failures (Table II, Fig. 1). In particular, the longest mean survival time was with MTX and shortest with leflunomide. These findings corroborate with the observations in a meta-analysis,[17] which concluded that RA patients stay significantly longer on MTX than on other DMARDs. The need for additional DMARD therapies owing to insufficient efficacy contributed the most to treatment failure in patients on HCQ, while adverse effect-related treatment discontinuation was most commonly observed with SSZ (88.9%) and MTX (87.5%). These findings are in contrast to a previous study that reported that 59.1% of discontinuations of MTX therapy are due to adverse effects,[7] and a meta-analysis[11] that concluded that a lack of efficacy was the major cause of treatment withdrawals from HCQ and SSZ. Such variations in the reasons for treatment failure from different DMARDs may be due to differences in the patient and disease characteristics as well as study designs in the various studies. A systematic review reported a lower rate of termination of MTX (10%–37%) due to toxicity than SSZ (17%–52%) but a higher rate than HCQ (10%–14%), with gastrointestinal disorders (30.8%) and hepatotoxicity (18.5%) being the most common adverse events with MTX.[18] The most common types of adverse events observed with MTX included hepatotoxicity (37.5%) and myelosuppression (31.2%), while anaemia (20%) and rash (20%) were the most common events with SSZ.

In this study, DMARDs were prescribed in 98% of the patients, with an average of 1.8 DMARDs per patient during the course of therapy. Regardless of the past treatment status, combinations of DMARDs were used to initiate therapy in > 60% patients, with MTX + HCQ being the most commonly prescribed. This was in accordance with current treatment guidelines that focus on early initiation of combination therapy. Concomitant therapies such as NSAIDs, acetaminophen and steroids were also prescribed frequently in most of the patients. The median (IQR) durations of intake of the three most commonly prescribed DMARDs (MTX, HCQ and SSZ) were found to be statistically similar.

We also explored the effect of various confounding factors on treatment failure using Cox proportional hazard models (Table IV). As might be expected, the most important predictor of treatment failure was adverse events (OR 22.24; 95% CI 11.96, 41.34; $p < 0.05$). Wolfe et al,[19] in a comparative assessment of treatment failure and effectiveness of MTX and leflunomide, reported side effects as the major predictor of treatment failure with the two DMARDs used in their study. We did not observe any significant association with other variables such as age, gender, disease duration and concomitant therapies used. In a previous cohort study that evaluated the

influence of various factors on discontinuation of DMARDs, it was concluded that a longer RA disease duration does not appear to increase the risk of DMARD discontinuation, although high disease activity (as assessed by erythrocyte sedimentation rate) was associated with a higher likelihood of termination of DMARDs.[20]

A major limitation of the present study was its retrospective nature, and hence an exclusive use of reported data. This could be avoided by conducting a prospective observational randomised trial; however, in view of the drawbacks of such a study, including channelling bias and associated longevity, we found it feasible to conduct a retrospective study.

REFERENCES

1. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59:762-84.
2. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology (Oxford) 2008; 47:924-5.
3. [No authors listed]. Indian guidelines for the management of rheumatoid arthritis. J Assoc Physicians India 2002; 50:1207-18.
4. van der Heijden JW, Dijkmans BA, Scheper RJ, Jansen G. Drug Insight: resistance to methotrexate and other disease-modifying antirheumatic drugs—from bench to bedside. Nat Clin Pract Rheumatol 2007; 3:26-34.
5. Bingham S, Emery P. Resistant rheumatoid arthritis clinics- a necessary development? Rheumatology (Oxford) 2000; 39:2-5.
6. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol 1995; 9:619-32.
7. Bernatsky S, Ehrmann Feldman D. Discontinuation of methotrexate therapy in older patients with newly diagnosed rheumatoid arthritis: analysis of administrative health databases in Québec, Canada. Drugs Aging 2008; 25:879-84.
8. Alarcón GS, Tracy IC, Strand GM, Singh K, Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 1995; 54:708-12.
9. De La Mata J, Blanco FJ, Gomez-Renio JJ. Survival analysis of disease modifying antirheumatic drugs in Spanish rheumatoid arthritis patients. Ann Rheum Dis 1995; 54:881-5.
10. Nagashima M, Shu G, Yamamoto K, Yamahatsu S, Yoshino S. The ability of disease modifying antirheumatic drugs to induce and maintain improvement in patients with rheumatoid arthritis. epidemiology of DMARDs treatment in Japan. Clin Exp Rheumatol 2005; 23:27-35.
11. Griffiths B, Situnayake RD, Clark B, et al. Racial origin and its effect on disease expression and HLA-DRB1 types in patients with rheumatoid arthritis: a matched cross-sectional study. Rheumatology (Oxford) 2000; 39:857-64.
12. Cronstein BN. Pharmacogenetics in the rheumatic diseases. Bull NYU Hosp Jt Dis 2006; 64:16-9.
13. Taniguchi A, Urano W, Tanaka E, Kamatani N. [Pharmacogenomics of antirheumatic drugs and personalized medicine for rheumatoid arthritis]. Nippon Rinsho 2007; 65:371-9. Japanese.
14. Ranganathan P. Pharmacogenetics of therapies in rheumatoid arthritis. Drugs Today (Barc) 2005; 41:799-814.
15. Tanaka E, Taniguchi A, Urano W, Yamanaka H, Kamatani N. Pharmacogenetics of disease-modifying anti-rheumatic drugs. Best Pract Res Clin Rheumatol 2004; 18:233-47.
16. Taniguchi A, Urano W, Tanaka E, et al. [Pharmacogenetics of disease modifying anti-rheumatic drugs]. Nippon Rinsho 2002; 60: 2339-44. Japanese.
17. Maetzel A, Wong A, Strand V, et al. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2000; 39:975-81.
18. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009; 68:1100-4.
19. Wolfe F, Michaud K, Stephenson B, Doyle J. Toward a definition and method of assessment of treatment failure and treatment effectiveness: the case of leflunomide versus methotrexate. J Rheumatol 2003; 30:1725-32.
20. Maradit-Kremers H, Nicola PJ, Crowson CS, O'Fallon WM, Gabriel SE. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: a population-based incidence cohort of patients with rheumatoid arthritis. J Rheumatol 2006; 33:248-55.