ScienceDirect

Available online at www.indianjrheumatol.com and www.sciencedirect.com

Rheumatology reviews

Sukhbir Uppal

Department of Medicine, University Hospital Sharjah, United Arab Emirates

1. Rheumatoid arthritis

1.1. *Women with RA have a two-fold increased risk of death compared to women without RA: 34 year follow up of 121,700 women*

RA has been associated with increased mortality compared to general population estimates. The authors of this paper evaluated mortality among women followed prospectively prior to RA diagnosis, directly comparing to women without RA. They conducted a study of RA and mortality among 121,700 women followed from 1976 to 2010 in the Nurses' Health Study (NHS). Models were adjusted for age, demographics and other mortality factors, including physical activity, smoking, obesity, comorbidities, and family history of cancer, CVD, and diabetes. The authors validated 960 incident RA cases and identified 25,699 deaths in 34 years of NHS follow-up. Of the 261 deaths among women with RA, 75 (29%) were from cancer, 58 (22%) were from CVD, and 43 (16%) were from respiratory causes. Compared to women without RA, women with RA had increased all-cause mortality that remained significant after adjusting for age and other mortality factors (HR 2.07, 95% CI 1.83–2.35). Mortality was significantly increased for seropositive (HR 2.33, 95% CI 2.00–2.71) and seronegative RA (HR 1.60, 95% CI 1.30–1.98) compared to non-RA women. Each five years of RA duration conferred a 32% (95% CI 27–36%) increased mortality compared to non-RA. Women with RA had significantly increased risk for mortality from CVD (HR 1.87, 95% CI 1.44–2.43), cancer (HR 1.35, 95% CI 1.07–1.69) and respiratory (HR 4.50, 95% CI 3.28–6.17) causes compared to women without RA. Respiratory mortality for women with seropositive RA was six-fold higher than non-RA women (HR 6.23, 95% CI 4.38–8.85).

Thus, in 34 years of prospective follow-up, women diagnosed with RA have a two-fold increased risk of death from any cause compared to women without RA. Respiratory mortality is six-fold higher in seropositive RA and women with RA are significantly more likely to die from CVD and cancer than women without RA. Respiratory mortality appears to be an important but understudied cause of death in RA. These findings provide evidence of high RA mortality burden that is unexplained by traditional mortality predictors. (ACR 2014 Abstract 818)

1.2. *70% RA patients discontinue their first biologic in 3 years*

Adherence and persistence to treatment is a cornerstone of treatment success in chronic diseases such as RA. The purpose of this study was to describe biologic treatment discontinuation and assess the predictors of discontinuation in RA patients followed at a Canadian clinic.

In this prospective cohort study, adult patients included in the RHUMADATA computerized database with a diagnosis of RA and treated with at least one biologic agent since 2003 were selected. Patients were followed for three years after therapy initiation or until treatment discontinuation. Biologic therapies considered include abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and anakinra.

A total of 623 eligible patients were treated with at least one biologic. The average time on treatment for the first biologic agent was 1.7 years. In all, 233 (37%), 326 (52%), 405 (65%), and 438 (70%) patients had stopped their first biologic treatment after 6, 12, 24, and 36 months, respectively. In time-to-event analyses, type of work [part time vs. full time; hazard ratio (HR): 1.57; 95% confidence interval (CI): 1.05–2.34] and income [$20,000 to $40,000 vs. less than $20,000 (HR: 1.35; 1.01–1.80) and $80,000 to $100,000 vs. less than $20,000 (HR: 2.16; 1.23–3.80)] were significantly associated with biologic discontinuation over the complete treatment duration. The number of DMARDs used (HR: 0.89; 0.80–0.99) and the use of methotrexate (yes vs. no; HR: 0.80; 0.64–0.99) were associated with a reduced risk of biologic discontinuation.

Thus, in this real-life Canadian study, high biologic discontinuation rates were observed over three years. This study also suggests that many clinical and socioeconomic variables are predictors of biologic therapy discontinuation in RA patients. (ACR 2014 Abstract 499)

E-mail address: uppalss@hotmail.com.
http://dx.doi.org/10.1016/j.injr.2015.01.005

Please cite this article in press as: Uppal S, Rheumatology reviews, Indian Journal of Rheumatology (2015), http://dx.doi.org/10.1016/j.injr.2015.01.005

1.3. *Abatacept, Adalimumab, Etanercept and Infliximab have similar retention rates as first line agents in patients with rheumatoid arthritis who are methotrexate inadequate responders*

The order of use of biologic agents is still a question for debate. Phase III trial data in MTX-IR patients show comparable efficacy results across biologic agents. This study aimed to assess if patients with RA treated with abatacept after failure of a first line agent (MTX-IR) have a different drug survival rate than patients similarly treated with adalimumab, etanercept or infliximab.

RA patients prescribed a first biologic agent after January 1st 2007 were included in the present analysis. We extracted a cohort formed of all patients prescribed abatacept (ABA), adalimumab (ADA), etanercept (ETA) or infliximab (INF) as their first biologic agent. A total 340 patients were included in the cohort. The 5 year retention rate of ABA, ADA, ETA and INF post MTX failure were 64%, 40%, 49% and 42% without significant statistical differences (Log-Rank $p = 0.29$).

Thus, abatacept, adalimumab, etanercept and infliximab after MTX failure have similar 5-years retention rates. (ACR 2014 Abstract 1536)

1.4. *In RA patients having failed their first anti-TNF agent, Tocilizumab, an IL-6 inhibitor, has better retention rates than a second anti-TNF agent: comparison with Adalimumab, Etanercept and Infliximab*

Tocilizumab, as an intravenous agent, has been approved for RA in 2010. It has been demonstrated effective in the treatment of RA either in monotherapy or combo therapy after non-biologic or biologic DMARDS. This paper describes its effectiveness in patients with RA failing a first anti-TNF DMARD and to compare its retention rate versus adalimumab, etanercept and infliximab in the same clinical situation.

All patients with RA having failed a first anti-TNF agent and subsequently exposed to tocilizumab after the 1st of January 2005 were extracted from the Rhumadata® database. 4 cohorts were created: One cohort of patients starting tocilizumab and 3 other cohorts starting either adalimumab, etanercept or infliximab. The data from 259 patients prescribed either tocilizumab (53 = 20%), adalimumab (97 = 37%), etanercept (82 = 33%) or infliximab (27 = 10%) as a second biologic agent were extracted from the Rhumadata® registry and clinical database. The four year retention rates of tocilizumab, adalimumab, etanercept and infliximab as second line biologic agents were 44.3%, 27.2%, 37.1% and 34.0% respectively. Kaplan–Meier survival analysis revealed significant differences in the drug retention rates (logrank $p = 0.0249$).

Thus, in RA patient having failed their first anti-TNF agent, tocilizumab, an IL-6 inhibitor, could be a more valuable alternative than cycling to a second anti-TNF agent. (ACR 2014 Abstract 502)

1.5. *Etanercept biosimilar (HD203) is as effective as etanercept (Enbrel®), in combination with methotrexate (MTX) in patients with RA*

Etanercept is a recombinant fusion protein that blocks TNF activity. HD203 is a biosimilar of etanercept. The aim of this study was to evaluate the equivalence in efficacy and to compare the safety of HD203 (biosimilar etanercept) and a reference etanercept, in combination with MTX in patients with RA.

Patients with active RA were randomly assigned (1:1) to 25 mg HD203 or reference etanercept, administered subcutaneously twice weekly with MTX for 48 weeks. In total, 294 patients were randomized: 147 to HD203 and 147 to reference etanercept. The proportion of patients achieving ACR20 at week 24 (primary endpoint) was not significantly different for HD203 and reference etanercept and equivalence in efficacy was demonstrated within predefined margins. In addition, there were no statistically significant differences between proportions achieving ACR20 at weeks 12 and 48. Similar trends were seen for ACR50 and ACR70, however the proportion of patients achieving ACR50 at week 24 and 48 was higher with HD203 than with reference etanercept. There were no statistically significant differences between the groups for ACRn, change in DAS28, and EULAR response at week 24 and 48.

Analysis of the safety set (HD203, $n = 147$; reference etanercept, $n = 146$) revealed no statistically significant difference in the number of treatment-emergent (all-causality) adverse events (AEs): HD203 76.87% vs. reference etanercept 78.08% ($p = 0.8040$). Furthermore, no statistically significant differences between HD203 and reference etanercept were observed with regards to adverse drug reactions, serious AEs, or discontinuations due to AEs. No unexpected AEs were observed, and few patients tested positive for anti-drug antibodies.

Thus, the study met the primary endpoint of demonstrating equivalence in efficacy of HD203 compared with a reference etanercept. HD203 was well tolerated, with a safety profile comparable to that of the reference etanercept in this population of Korean patients with RA. (ACR 2014 Abstract 2825)

1.6. *Reducing therapy in RA patients in remission is feasible in a subset of patients*

Due to improved therapeutic management a steadily increasing number of RA patients reach stable remission of disease. Data on withdrawal of medication after sustained remission are limited, though it is important for economic and safety reasons. The RETRO study represents a real-life study addressing different strategies of reduction of DMARD therapy in RA patients in disease remission. The aim of the study was to evaluate the possibility of tapering and even discontinuation of DMARD therapy in RA patients in stable long-lasting remission and to determine predictors for recurrence of disease.

In this phase 3 trial, patients with RA of ≥12 months were enrolled into the study if they were in clinical remission (DAS28-ESR < 2.6) at stable dose of DMARDs for more than 6 months. Patients on ≥1 conventional and/or biological DMARDs were included and randomized into three trial arms: Arm 1 (control group) was continuing full-dose conventional and/or biological DMARD treatment for 12 months; arm 2 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 12 months and arm 3 was

Please cite this article in press as: Uppal S, Rheumatology reviews, Indian Journal of Rheumatology (2015), http://dx.doi.org/10.1016/j.injr.2015.01.005