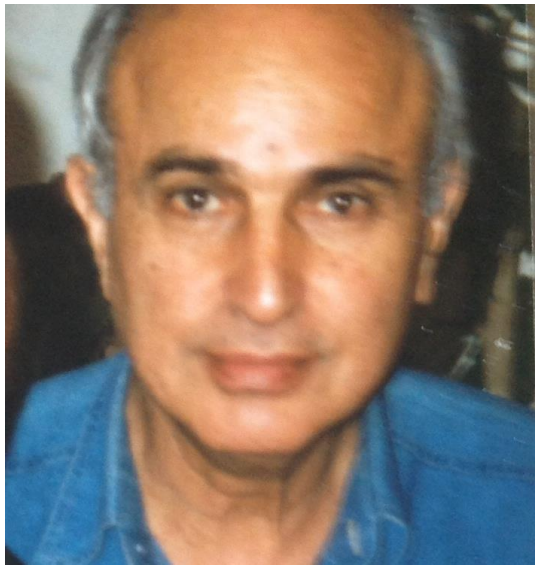
Follow up of patients on biologics or small molecules



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The day after remission

Is it really cost effective to continue biologic therapy?

Real World Evidence for Effectiveness of Biologics for Rheumatoid Arthritis

Systematic Literature Review of Population Based Registry Studies

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- Objectives: To assess real-world effectiveness of biologics for RA using systematic review of large population based registries. Methods: A systematic literature search for full text publications was conducted using Pubmed and Embase for registry based RA studies for biologics. Data were collected for the study type, country, registry name, number of patients, follow up (years), methods and key findings. Descriptive
- analyses were conducted to summarize overall effectiveness of biologic treatments. Results: Of 850 search results, 18 studies met the inclusion criteria. These registry studies analyzed data for 16,538 patients over a median follow up of 2 years (range: 0.5-10 years). Seven of 18 studies were in registries with 1000+ patients (n= 11,344). Geographically, registries covered many regions such as Japan (4), Europe (3), USA (2), Canada (1), Denmark (1), France (1), Korea (1), Spain (1) and Sweden (1). The
- longest follow up study (10+ years) was an analysis of the Corrona registry (n= 1791), showing that in biologic naive patients treated with adalimumab, the initial improvements in remission and PRO assessments were sustained in those patients who remained on adalimumab over 10 years of follow-up. Additional studies demonstrated similar effectiveness of biologic therapies, factors driving adherence and role of concomitant methotrexate. A cost effectiveness analysis using data from Swedish Rheumatology Registers (n= 2,558), showed that incremental cost effectiveness ratio (ICER) for anti-TNFs ranged from € 50,000-120,000, with lower estimates for combination with methotrexate and as a first biologic
- Conclusions: Real-world evidence registry based studies demonstrates long term effectiveness of biologics for RA.

Is there any evidence to support biologic tapering?

Dierckx et al. Arthritis Research & Therapy (2020) 22:96
https://doi.org/10.1186/s13075-020-02165-4

Arthritis Research & Therapy

Tapering of biological antirheumatic drugs in rheumatoid arthritis patients is achievable and cost-effective in daily clinical practice: data from the Brussels UCLouvain RA Cohort

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- Studies have demonstrated that rheumatoid arthritis (RA) patients who achieve low disease activity or remission are able to taper biological disease-modifying antirheumatic drugs (bDMARDs)
- The aim of this study was to evaluate the proportion of patients in whom bDMARDs can be tapered in daily practice and to analyze the characteristics of these patients. Other objectives were to analyse which bDMARDs are more suitable for dose reduction and the cost savings
- Pts who had received biologics from 2000 till 2018 were analyzed retrospectively

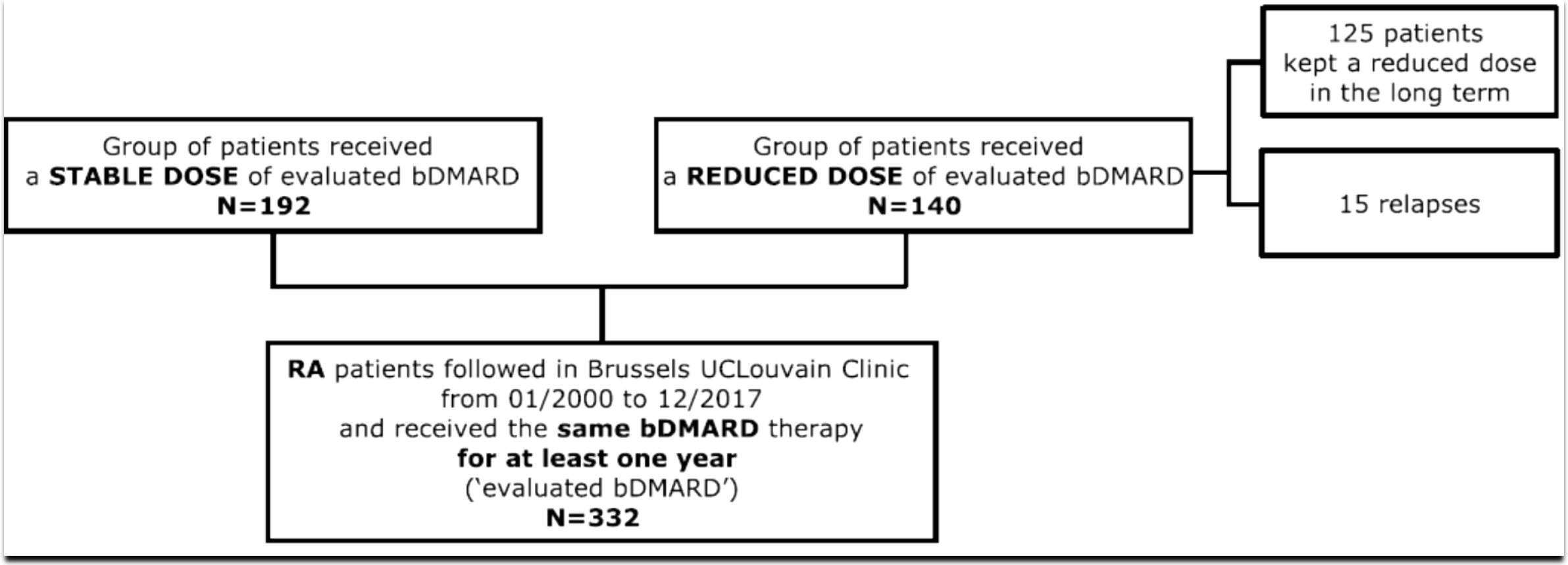
Tapering of biological antirheumatic drugs in rheumatoid arthritis data from the Brussels UCLouvain RA Cohort

Results

Data from 332 eligible RA patients from our Brussels UCLouvain cohort were retrospectively analysed; 140 patients (42.1%) received a tapered regimen, and 192 received stable doses of bDMARDs. The age at diagnosis (43.1 vs 38.7 years, p = 0.04), HAQ score (1.3 vs 1.5, p = 0.048), RF positivity rate (83.3 vs 72.9%, p = 0.04) and disease duration at the time of bDMARD introduction (9.7 vs 12.1 years, p = 0.034) were significantly different between the reduced-dose and stable-dose groups

- Interestingly, relatively more patients receiving a tapered dose were treated with a combination of bDMARDs and methotrexate (MTX) (86.7% vs 73.8%, p = 0.005). In our cohort, anti-TNF agents were the most commonly prescribed medications (68%). Only 15 patients experienced a flare during follow-up. Adalimumab, etanercept and rituximab were the most common bDMARDs in the reduced-dose group and were associated with the most important reductions in annual cost

data from the Brussels UCLouvain RA Cohort



Shall we consider some patients for a biologic free period?

Relapse in rheumatoid arthritis patients undergoing dose reduction and withdrawal of biologics

are predictable factors more relevant than predictive parameter An observational prospective real-life study

Objective :To determine predictive/predictable factors of relapse in rheumatoid arthritis (RA) patients undergoing biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) dose reduction/discontinuation.

Patients and methods: RA patients receiving the same bDMARD for more than 1 year, in Simplified Disease Activity Index (SDAI) remission, were selected in an observational monocentric real-life study. The 18-month follow-up included spacing (6 months) and withdrawal (12 months) periods of bDMARD. Clinical, biological and ultrasonographic (US) parameters were collected regularly.

Relapse was defined by SDAI>11.

Vittecoq O, *et al. BMJ Open* 2019;9:e031467. doi:10.1136/bmjopen-2019-031467

BMJ Open

Relapse in rheumatoid arthritis patients undergoing dose reduction and withdrawal of biologics

Results

- Fifty-three RA patients (mean age: 58 years;72% women; median duration: 11 years) were enrolled. Forty-two received bDMARD anti TNF(n=39) or anti IL6r (n=3) and 11 were treated by abatacept. The number of relapses during the spacing and discontinuation periods were 19 and 20, respectively. After 18 months of follow-up, among the 53 patients, 12 maintained bDMARD-free remission, 39 had relapsed and 2 were lost of follow-up. Median time to relapse was 11.8 months
- In multivariate analysis, baseline factors predictive of relapse were corticosteroid intake, female gender, longer disease duration and no methotrexate intake with bDMARD. Concerning the survival analysis, also taking into account the factors of predictability, the main risk factor of relapse after discontinuation was an increase of SDAI >0 during the spacing period (p=0.03). US findings were not contributive.
- Conclusion: In the context of RA in remission under bDMARDs, variation of SDAI during the dose-reduction phase is more relevant than baseline parameters to predict success of drug withdrawal

Clinical guidelines for tapering of biologics in RA

American College of Rheumatology(ACR) 2015 (Singhet al., 2015b)

Recommendation	Commentary
If patient in remission, taper DMARD, TNF or non-TNF biologic and tofacitinib Do not discontinue all RA therapies If disease activity is low, continue DMARD therapy, TNF or non-TNF biologic or tofacitinib rather than discontinuing	Very-low-quality evidence. Insufficient difference in efficacy between non-TNF biologics and tofacitinib to outweigh the long-term safety data and the amount of experience associated with non-TNF biologics

European League Against Rheumatism (EULAR)2017 (Smolen et al.,2017)

Recommendation	Commentary
If a patient is in persistent remission after having tapered steroids, consider tapering biologic, especially if combined with a DMARD	Tapering means reduction of dose or increase in dosing interval, and does not necessarily imply discontinuation of biologic. Tapering and stopping of biologic monotherapy not yet sufficiently studied

Clinical guidelines for tapering of biologics in RA

APLAR

Guideline	Recommendation	Commentary
Asia Pacific League of Associations for Rheumatology (APLAR) 2015 (Lau et al., 2015)	In patients who have achieved remission, a reduction in treatment should be considered. If the patient remains in remission >12 months, tapering of biologic can be considered	Withdrawal after remission is reached remains inadequately researched but, given the cost implications for many people with RA in the region, many request tapering, and it can be considered pending further data

Factors which increase risk of RA flare after tapering biologics

Disease activity	DAS28 correlated with sustained remission in univariate and multivariate analyses (OR 0.143, 95% CI 0.029, 0.711) (Tanaka et al., 2015). Lower simple disease activity index scores associated with maintenance of remission after discontinuing etanercept (Yamanaka et al., 2016).
Baseline functional disability (on the health assessment questionnaire)	HR 2.07 (95% CI 1.23, 3.49) after adjustment for potential confounding factors, including DAS28, RF and anti-CCP status, C-reactive protein, treatment arm, morning stiffness, pain intensity, patient global assessment and smoking status (Fautrel et al., 2016).
RF status	HR 1.99 (95% CI 1.03, 3.83), after adjustment for potential confounding factors, including DAS28, HAQ, anti-CCP status, C-reactive protein, treatment arm, morning stiffness duration, pain intensity, patient global assessment,and smoking status (Fautrel et al., 2016). Negative RF associated with successful discontinuation of tocilizumab (Kaneko et al., 2018)
Anti-CCP antibodies	Multivariate logistic regression identified anti-CCP positivity in comparison with continuation as predictors for relapse (Haschka et al., 2016).
Drug concentrations	Inverse correlation between lower etanercept drug levels and a higher chance for successful dose reduction (AUC 0.36, 95% CI 0.23, 0.49; cut-off <2.6 mg/L); higher adalimumab trough concentrations predicted successful dose reduction (AUC 0.86, 95% CI 0.58, 1.00; cut-off >7.8) (Bouman et al., 2017) RA patients with trough adalimumab concentrations >8 µg/ml could prolong dosing interval to once every 3 weeks without loss of disease control (l'Ami et al., 2018)
Patient global rating	Lower patient global rating of well-being associated with successful discontinuation of tocilizumab (Kaneko et al., 2018)
Ultrasound detected synovitis	Presence of ultrasound-detected synovitis associated with tapering failure (Naredo et al., 2015)

Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study

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Ann Rheum Dis: first published as 10.1136/annrheumdis-2018-214970 on 6 April 2019.

Objectives: The aim of this study is to evaluate th effectiveness of two tapering strategies after achieving controlled disease in patients with rheumatoid arthritis(RA), during 1 year of follow-up

Methods: In this multicentre single-blinded (research nurses) randomised controlled trial, patients with RA were included who achieved controlled disease, define as a (DAS) ≤ 2.4 and a Swollen Joint Count (SJC) ≤ 1, treated with both a conventional synthetic (csDMARD) and a TNF inhibitor

Eligible patients were randomised into gradual tapering csDMARDs or TNF inhibitors. Medication was tapered if the RA was still under control, by cutting the dosage into half, a quarter and thereafter it was stopped. Primary outcome was proportion of patients with a disease flare, defined as DAS > 2.4 and/or SJC > 1

Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with RA

- Results: A total of 189 patients were randomly assigned to tapering csDMARDs (n = 94) or tapering anti-TNF (n = 95). The cumulative flare rates in the csDMARD and anti-TNF tapering group were, respectively, 33 % (95% CI,24% to 43 %) and 43 % (95% CI, 33% to 53 % (p = 0.17). Mean DAS, HAQ-DI and EQ-5D did not differ between tapering groups after 1 year and over time
- Conclusion: Up to 9 months, flare rates of tapering csDMARDs or TNF inhibitors were similar. After 1 year, a non-significant difference was found of 10 % favouring csDMARD tapering. Tapering TNF inhibitors was, therefore, not superior to tapering csDMARDs. From a societal perspective, it would be sensible to taper the TNF inhibitor first, because of possible cost reductions and less long-term side effects

American College of Rheumatology
Empowering Rheumatology Professionals
MEETING ABSTRACTS

Tapering TNF Inhibitors in Axial Spondyloarthritis: Systematic analysis of the literature and meta-Analysis

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- **Background/Purpose:** Tumor necrosis factor inhibitors (TNFi) are effective in treating patients with axial spondyloarthritis (axSpA), but they are associated with adverse effects and high costs. According to the ASAS-EULAR recommendations, if patients are in sustained remission or low disease activity, tapering of TNFi can considered.
- We aimed to assess the risk of relapse after TNFi tapering strategies compared to standard dose continuation in patients with axSpA.
- **Methods:** We conducted a systematic search of the literature using Medline, Embase and Cochrane databases up to 27 February 2018. All randomized controlled trials (RCTs) and controlled cohort studies (CCTs) comparing the rate of relapse in patients with tapering dose versus standard dose of TNFi after achieving remission or low disease activity were selected. For the meta-analysis, the estimated event was the number of patients who had relapsed or not maintained remission or low disease activity in each treatment group (tapering versus standard dose). Data were extracted independently by two investigators. A global risk ratio (RR) was estimated using an inverse variance approach with fixed or random effect model, according to the level of heterogeneity (I2, Cochran's Q-test). All these computations were performed using RevMan 5.3 software with a p-value threshold of 0.05

Tapering TNF Inhibitors in Axial Spondyloarthritis: Systematic analysis of the literature and meta-Analysis

Results

- Among the 544 publications screened, 5 studies (3 RCTs including one available only as abstract and 2 CCTs) were included, involving 230 patients who tapered TNFi dose and 226 treated with standard dose. Clinical heterogeneity between the trials was low: mean age between 46.0 and 46.7 years, male: 72.6% – 87.2%, ankylosing spondylitis according to modified New York criteria: 74% – 100%, HLA-B27 positive: 91.0% – 93.0%. Methodological heterogeneity between the trials was high: all tapering modalities, relapse definitions, duration of the follow-up and evaluation times were different. None of tapering strategies were disease activity guided.
- Tapering TNFi dose was not associated with a statistically significant increase of relapse (RR [95% CI] = 1.51 [0.99 to 2.31], p = 0.05 in comparison with standard dose continuation. A relapse was observed in 22.2% of patients who tapered TNFi versus 13.3% in patients with standard doses.

Alternative dosing for Rituximab

Low-dose regimens

- Evidence comparing the benefits of low and high dose Rituximab in combination with MTX was analyzed in a 2014 systematic review and meta-analysis of reports
- Six randomized trials and two cohort studies met inclusion criteria, and four of the randomized trials, including a total of 1308 patients, were included in the meta-analysis of efficacy outcomes
- The majority of the patients included in these trials had not previously been treated with TNF inhibitors
- The meta-analysis found no statistically significant difference between low-dose (500 mg given twice) and high-dose (1000 mg given twice) treatments at 24 and 48 weeks in most of the composite measures of disease activity ACR20, ACR50, ACR70, and Disease Activity Score in 28 joints [DAS28]), or in patient-reported HAQ scores
- Trends that did not achieve statistical significance but favored high-dose rituximab were found for the ACR70 at 24 weeks

cont'd

- A subsequent observational cohort study of patients in national registries, which analyzed data from 2625 patients treated with rituximab using two doses of 1000 mg and 248 patients treated with two doses of 500 mg, described comparable improvements in DAS28 scores and EULAR response rates in the two groups at six months following the first course of rituximab treatment
- Lower doses of rituximab may also be effective for the retreatment of patients who have responded to usual initial therapy, while limited data suggest that initial therapy with a higher-dose regimen may be beneficial in patients with incomplete B cell depletion following the first infusion
- the Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial compared a regimen of rituximab 1000 mg given twice with a lower dose (500 mg given twice) in 465 patients with RA refractory to methotrexate alone
- There was no difference between the two groups in the proportion of patients who achieved an ACR20 response (54 and 55 percent)
- However, the 1000 mg regimen was associated with significant increases in the proportion of patients achieving an ACR70 response (20 versus 13 percent) or EULAR "good" response (28 versus 14 percent)

ULTRA-LOW DOSES OF RITUXIMAB or RETREATMENT OF RHEUMATOID ARTHRITIS: A RANDOMISED CONTROLLED NON-INFERIORITY TRIAL

- **Background** Rituximab (RTX) is an effective treatment for patients with Rheumatoid Arthritis (RA). 1000mg (1 × 1000mg or 2 × 500mg) has similar 6-month efficacy as the registered dose of 2 × 1000mg. Based on several case reports and a case series even lower doses might be sufficient for maintenance treatment, potentially improving safety and decreasing costs
- **Objectives** To compare effectiveness of RTX retreatment with ultra-low doses (1 × 500mg or 1 × 200mg) to standard low dose (1 × 1000mg)
- **Methods** A 6-month double-blind randomised controlled non-inferiority trial (REDO study (2)) was performed in 5 centres in the Netherlands. Patients with RA responding well to RTX (based on DAS28-CRP<2.9 or clinical judgement) were randomised (1:2:2) to 1 × 1000mg, 1 × 500mg or 1 × 200mg RTX respectively. DAS28-CRP and peripheral CD20+ B-cells were measured at baseline, 3 and 6 months. Primary analysis (per protocol with LOCF) consisted of a hierarchical testing procedure comparing ultra-low doses (1 × 500mg at 3 and 6 months, then 1 × 200mg at 3 and 6 months) to 1 × 1000mg using a non-inferiority margin of 0.6 (on DAS28-CRP). DAS28-CRP change of study groups was compared using linear regression, adjusted for baseline DAS28-CRP, RF/ACPA status and concomitant csDMARD use.

Results

- The projected inclusion was met (n=142). In both ultra-low dose groups 2 patients received an extra dose of 1000mg RTX due to a flare. The 500mg dose was non-inferior to 1000mg at 3 months (-0.04 (95% CI -0.39 to 0.30)), but not at 6 months (0.31 (95% CI -0.05 to 0.68)
- The 200mg dose was non-inferior to 1000mg at both time points. Because of our pre-defined hierarchical testing, non-inferiority could not formally be inferred for the 200mg dose
- Mean DAS28-CRP scores remained low in all groups throughout the study, and B-cell counts decreased similarly at 3 months
- In the 200mg group, more patients received intramuscular corticosteroid injection(s) compared to the 1000mg group

L.M. Verhoef1, Nathan den Broeder2, R.M. Thurlings3, W.H. van der Laan4, W. van der Weele5, Marc Kok5, H.J. Bernelot Moens5, Thasia Woodworth5, Bart van den Bemt6, Frank van den Hoogen5, Alfons den Broeder5 Annals of rheumatic diseaseVolume 78, Issue Suppl 2. June 2019

What if my patient develop a malignancy on long term biologic therapy?

Risk of Malignancies in Pts with RA Treated with Rituximab: Analyses of Global Post marketing Safety Data and Long-Term Clinical Trial Data

Introduction: Patients with (RA) are at an increased risk of developing malignancies, but it is unclear whether this increased risk is the result of disease pathobiology or immunosuppressant treatments for RA. This analysis evaluated the potential risk of malignancy in patients with RA treated with rituximab (MabThera®/Rituxan®) manufactured by F. Hoffmann-La Roche Ltd.

Methods: Malignancy rates were obtained from the rituximab global company safety database for adverse event reporting and from the rituximab global clinical trial program for RA consisting of eight randomized clinical trials, two long-term open-label extensions, and one open-label prospective study. Global company safety database searches were performed using the standard Medical Dictionary for Regulatory Activities (MedDRA) queries “Malignant tumors wide” and “Skin malignant tumors wide” up to April 30, 2017. Age- and sex-specific comparator values from the general population were obtained from the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database.

Results: For the 409,706 patients with RA in the rituximab global company safety database since first market approval in 2006, 1739 cumulative malignant events were reported, with an overall malignancy reporting rate of approximately 4.2 events per 1000 patients. No evidence of increased risk of malignancy, of any organ-specific type, was found following rituximab treatment. The rate of malignancies from rituximab-treated patients in RA clinical trials was 7.4 per 1000 patient-years. This is within the expected range, with no evidence for increased risk over time or with additional rituximab courses.

Conclusions: Analyses of the global postmarketing safety database and long-term clinical trial data showed no evidence of an increased risk of malignancy of any type following rituximab treatment in patients with RA

Published: 21 November 2019 Paul Emery, Daniel E. Furst, Petra Kirchner, Simone Melega, Stuart Lacey & Patricia B. Lehane Rheumatology and Therapy volume 7, pages121–131(2020)

Results

- For the 409,706 patients with RA in the rituximab global company safety database since first market approval in 2006, 1739 cumulative malignant events were reported, with an overall malignancy reporting rate of approximately 4.2 events per 1000 patients. No evidence of increased risk of malignancy, of any organ-specific type, was found following rituximab treatment. The rate of malignancies from rituximab-treated patients in RA clinical trials was 7.4 per 1000 patient-years. This is within the expected range, with no evidence for increased risk over time or with additional rituximab courses.

Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register

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- Anti-tumour necrosis factor (TNF) therapy is a mainstay of treatment in rheumatoid arthritis (RA). In 2001, BSRBR was established to evaluate the safety of these agents. This paper addresses the safety of anti-TNF therapy in RA with specifi c reference to serious skin and soft tissue infections (SSSI) and shingles.

Methods A cohort of anti-TNF-treated patients was recruited alongside a comparator group with active RA treated with non-biological disease-modifying antirheumatic drugs (nbDMARD). 11 881 anti-TNF and 3673 nbDMARD patients were analysed. Follow-up was by 6-monthly questionnaires to patients and clinicians. Analyses considered SSSI and shingles separately. Incidence rates (IR) were calculated and then compared using survival analyses.

Results

- The crude IR for SSSI were: anti-TNF 1.6/100 patient-years (95% CI 1.4 to 1.8); nbDMARD 0.7/100 patient-years (95% CI 0.5 to 1.0) and shingles: anti-TNF 1.6/100 patient-years (95% CI 1.3 to 2.0); nbDMARD 0.8/100 patient-years (95% CI 0.6 to 1.1). Adjusted HR were SSSI 1.4 (95% CI 0.9 to 2.4), shingles 1.8 (95% CI 1.2 to 2.8). For SSSI, no significant differences were seen between anti-TNF agents
- For shingles, the lowest risk was observed for adalimumab (adjusted HR vs nbDMARD) 1.5 (95% CI 1.1 to 2.0) and highest for infliximab (HR 2.2; 95% CI 1.4 to 3.4)).
- **Conclusion:** A significantly increased risk of shingles was observed in the anti-TNF-treated cohort. The risk of SSSI tended towards being greater with anti-TNF treatment but was not statistically significant. As with any observational dataset cause and effect cannot be established with certainty as residual confounding may remain. This finding would support the evaluation of zoster vaccination in this population

published in24 April 2012

Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

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BACKGROUND & AIMS: We performed a systematic review and meta-analysis to evaluate the comparative risk of serious infections with tumor necrosis factor (TNF) antagonists, non-TNF targeted biologics, tofacitinib, and immunosuppressive agents in patients with inflammatory bowel diseases (IBDs).

METHODS: In a systematic search of publications, through March 18, 2018, we identified 15 observational studies (>500 person-years) of patients with IBD treated with TNF antagonists, non-TNF targeted biologics, tofacitinib, and/or immunosuppressive agents (thiopurines, methotrexate) that reported risk of serious infections. Only studies with active comparators were included, to allow appropriate comparative synthesis. We performed random-effects meta-analysis and estimated relative risk (RR) and 95% CIs.

Results

clinical Gastroenterology and Hepatology 2019

Compared with anti-TNF monotherapy, risk of serious infection increased with the combination of anti-TNF and an immunosuppressive agent (in 6 cohorts: RR, 1.19; 95% CI, 1.03–1.37), with anti-TNF and a corticosteroid (in 4 cohorts: RR, 1.64; 95% CI, 1.33–2.03), or with all 3 drugs (I 2 cohorts: RR, 1.35; 95% CI, 1.04–1.77) there was minimal heterogeneity among studies

In contrast, monotherapy with an immunosuppressive agent was associated with a lower risk of serious infections than monotherapy with a TNF antagonist (7 cohorts: RR, 0.61; 95% CI 0.44– 0.84) or a TNF antagonist with an immunosuppressive agent (2 cohorts: RR, 0.56; 95% CI, 0.39– 0.81)

Infliximab-based therapy was associated with a lower risk of serious infections compared with adalimumab-based therapy in patients with ulcerative colitis (4 cohorts: RR, 0.57; 95% CI, 0.33–0.97), but not Crohn's disease (4 cohorts: RR, 0.91; 95% CI, 0.49–1.70) Few data were available on the comparative safety of biologic agents that do not inhibit TNF and tofacitinib.

CONCLUSIONS: Combination therapies for IBD that include TNF antagonists, especially with corticosteroids, are associated with a higher risk of serious infection, whereas monotherapy with an immunosuppressive agent is associated with a lower risk, compared with monotherapy with a TNF antagonist. Studies are needed to evaluate the comparative safety of non-TNF targeted biologics and small molecules for treatment of IBD.

Prevalence and Risk Factors of Serious Infections in Rheumatoid Arthritis Patients Receiving the Biologic/Targeted Synthetic Dmards: A Propensity Score Analysis from the Hong Kong Biologics Registry

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Methods:

Patients with RA included in the Hong Kong Biologics Registry since 2007 ever treated with b/tsDMARDs were studied. Data on withdrawal of b/tsDMARDs due to serious adverse events (SAEs) and SIs was analyzed. Demographic data, medical comorbidities (eg. diabetes mellitus, chronic lung, kidney and liver diseases) and concomitant use of glucocorticoids (GCs) and csDMARDs were retrieved and their contribution to SIs was evaluated by separate logistic regression. The propensity score for SIs was computed and patients were strati□ ed into 5 quintiles according to the risk. The hazard ratios (HRs) of SIs with respect to individual b/tsDMARDs in each quintile were studied by Cox regression. ACR meeting 2018

Results

- 2355 courses of b/tsDMARDs were used in 1355 Chinese patients with RA (83% women; mean age (54.0±12.7 years).
- The usage of various b/tsDMARDs was: adalimumab (12%), etanercept (24%), infliximab (17%), golimumab (9.4%), certolizumab (0.9%), tocilizumab (19%), rituximab (6.6%), abatacept (7.7%) and tofacitinib (2.7%). After a follow-up of 5056 patient-years, 1433 courses of b/tsDMARDs were discontinued, with major reasons being inefficacy (50%), SAEs (22.4%) and cost (8.4%).
- Among those b/tsDMARD courses terminated for SAEs, 32% were due to SIs (103 episodes)
- The rate of SIs was 1.17/100 patient-years. The commonest causes of SIs were pulmonary tuberculosis (TB) (41%), severe pneumonia (33%), soft tissue infection (6.8%), atypical TB (2.9%), urogenital sepsis (2.9%), septic arthritis (2.9%), hepatobiliary / gastrointestinal sepsis (2.9%), central nervous infection (1%), severe viral infections including herpes zoster (5.8%), and opportunistic infections(2.9%)
- TB infection was most frequent in users of infliximab(2.32/100 patient-years), followed by tofactinib (1.47), adalimumab (1.27), etanercept (0.62) and tocilizumab (0.36)

Which lab tests shall I request for biologic users in my routine practice ?

Review of Routine Laboratory Monitoring for Patients with Rheumatoid Arthritis Receiving Biologic or Nonbiologic DMARDs

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Biologic and Targeted Synthetic DMARDs: Liver and Lipid Monitoring

- Patients with RA have a 50% to 60% increased risk for CV-related death compared with the general population. Because of this increased risk, EULAR guidelines recommend that all patients with RA should undergo an annual CV risk assessment
- Addition of TC, LDL and HDL to routine laboratory tests and that the ratio of TC to HDL is the most stable marker of lipid-associated CV risk in RA
- Among the biologic and targeted synthetic DMARDs, tocilizumab and tofacitinib are the only ones for which specific recommendations for monitoring serum lipids and liver function are given
- According to the prescribing information, lipids (TC, triglycerides, LDLC, and/or HDL-C) should be measured 4 to 8 weeks after initiation for both tocilizumab and tofacitinib and every 24 weeks thereafter
- for tocilizumab ALT and AST levels should be measured 4 to 8 weeks after initiation and every 3 months thereafter. The prescribing information for tofacitinib states that there should be routine monitoring of all liver enzymes

Biologic and Targeted Synthetic DMARDs: Neutrophil and Platelet Count Monitoring

- Neutropenia has been linked to an increased risk of infection; however, cases of therapy-associated severe neutropenia have been observed without incidence of infection
- Biologic DMARDs are often associated with transient, sustained, or late-onset decreases in neutrophils and/or platelets
- The prescribing information for both tocilizumab and tofacitinib suggests monitoring of ANCs 4 to 8 weeks after initiation and every 3 months thereafter
- Reports of neutropenia in patients with autoimmune disease treated with rituximab are infrequent; however, late-onset neutropenia is reported in 1.3% to 5.8% of Pts
- For rituximab, continued monitoring of complete blood counts including ANCs, is recommended at 2- and 4-month intervals during rituximab therapy

Biologic and Targeted Synthetic DMARDs: Neutrophil and Platelet Count Monitoring

- Among studies reporting ANCs following biologic DMARDs, <1% of patients who received adalimumab or etanercept in combination with MTX were reported to experience grade 3 or 4 decreases
- In the pooled long-term (up to 4.6 years) safety analysis of the tocilizumab RA trials, 4.8% of patients experience grade 3 decreases in ANCs, and <1% of patient (14 out of 4009 observed patients) experienced grade 4 decreases in ANCs; 1 patient experienced a serious infection of empyema temporally associated with grade 3 neutropenia and no patients with grade 4 neutropenia experienced serious infection within 30 days of observed neutropenia
- In Phase III clinical trial, 1.1% to 1.6% of patients who receive tofacitinib experienced grade 2 or 3 neutropenia at month 3
- Although thrombocytopenia is an uncommon feature of RA, its occurrence may be associated with RA-related therapies. Although cases of drug induced thrombocytopenia have been associated with clinically important bleeding events

Renal function test

- For monitoring and assessment of kidney function, serum creatinine may be measured as opposed to creatinine clearance.
- The prescribing information for cyclosporine and tacrolimus both notes elevated serum creatinine following administration and recommends close monitoring of renal function
- Among the bDMARDs, only tofacitinib has prescribing information that reports drug-associated increases in serum creatinine levels
- The mean increase in serum creatinine in patients treated with tofacitinib in clinical trials was <0.1mg/dL over 12 months of treatment
- In the long-term extensions, however, up to 2% of patients discontinued tofacitinib due to an increase in creatinine > 50% above baseline. The clinical significance of the observed serum creatinine elevations is unknown

Initial screening

1. Full medical history including history of TB exposure, hepatitis B/hepatitis C/HIV, malignancy, smoking, any planned surgery, pregnancy status, previous phototherapy, history of immunosuppression in last 3/12
2. Clinical examination – malignancy, especially skin cancer, infection, congestive heart failure, and neurological symptoms
3. Determine vaccination status – vaccinations to be administered prior to commencing treatment (varicella serology if necessary); ensure screening for cervical cancer attended as per guidelines for female patients
4. Enter into a prospective safety registry
5. Blood tests: FBC, U&E, LFT, Beta hCG (females only), HIV, and hepatits panel
6. CXR and IGRA

IGRA/CXR positive for TB or history of exposure to TB then refer to respiratory physician for advice before initiation of chemoprophylaxis

At 3–6 monthly intervals or at clinical discretion monitor for:

1. Signs of infection
2. History of exposure to TB
3. Clinical examination Inc. skin assessment for malignancy and assessment of lymphadenopathy
4. Consider repeat FBC U & E and LFTs
5. Ensure female patients using appropriate contraception. Pregnancy test if necessary

Evidence of prior/current hepatitis B infection or hepatitis C positive then refer to gastroenterologist before commencing immunosuppression

At yearly follow-up:

As per 3–6 month follow-up, plus:

1. Ensure annual influenza vaccine
2. IGRA if history of TB exposure

PATIENT PERSPECTIVES ON TAPERING BIOLOGICS

To understand patient perspectives, it is important to characterize attributes that influence RA patient preferences around treatment changes in general.

A disconnect between patient satisfaction with therapy and physician disease and functional assessments has been observed, indicating that satisfaction with therapy involves much more than just achieving control of disease activity (Fraenkel, Seng, Cunningham, & Mattocks, 2015a; Wolfe & Michaud 2007)

Concerns about adverse effects for any class of antirheumatic medication, negative impacts of treatments on quality of life, and loss of disease control are all notable concerns for people with RA, and there is a preference for accepting the present status over changes to treatment that may lead to future improvement in disease control (Fraenkel, Matzko, et al., 2015b; Wolfe & Michaud, 2007)

Thank you