***Review Article***

***Title:***

Drug efficacy and safety of biologics and Janus kinase inhibitors in elderly patients with rheumatoid arthritis

***Author:***

Kosuke Ebina*

***Affiliations:***

Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, Osaka, Japan

There are no tables and figures

***Keywords:***

biologics, efficacy, elderly patient, Janus kinase inhibitors, rheumatoid arthritis, safety

***Corresponding author:*** E-mail: k-ebina@ort.med.osaka-u.ac.jp

**Abstract**

Elderly patients with rheumatoid arthritis (RA) are frequently associated with higher disease activity and impaired physical function, although they show intolerance for conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), because of their comorbidities (renal dysfunction, pulmonary disease, and others). However, the present treatment recommendation based on randomized controlled trials is not distinguished by age or comorbidities. Therefore, this review aimed to investigate the efficacy and safety of biological DMARDs

(bDMARDs) and Janus kinase inhibitors (JAKi) in elderly patients. Present bDMARDs, including tumor necrosis factor inhibitors (TNFi), cytotoxic T lymphocyte-associated antigen-4-immunoglobulin (CTLA4-Ig; abatacept), interleukin (IL)-6 receptor antibody (tocilizumab and salirumab), and anti-CD20 antibody (rituximab), may be similarly or slightly less effective or safe (probably because of comorbidities and intolerance to csDMARDs, such as MTX) in elderly patients compared with younger patients. Oral glucocorticoid (GC) use, prolonged disease duration, and very old patients appear to be associated with an increased risk of adverse events, such as serious infection. Some recent cohort studies demonstrated that non-TNFi showed better retention than TNFi in elderly patients (may be partially due to low dependency on csDMARDs such as MTX). Both TNFi and non-TNFi agents may not strongly influence the risk of adverse events such as cardiovascular events and malignancy in elderly patients. Regarding JAKi, the efficacy appears to be similar, although the safety (particularly for serious infections, including herpes zoster) may be attenuated by aging. After careful consideration of comorbidities, the tolerance for csDMARDs, and the balance between risk and benefit, the appropriate choice of bDMARDs or JAKi by each patient's background may be beneficial for the treatment of elderly patients who are difficult to treat with GC or csDMARDs. After the improvement of disease activity, a careful dose reduction of combined GC and csDMARDs as well as tapering or spacing of bDMARDs or JAKi may contribute to sustained safety.

## Introduction

In patients with rheumatoid arthritis (RA), the proportion of elderly individuals [1] and the onset age of RA are rapidly increasing [2]. Elderly patients with RA are associated with more comorbidities, such as chronic obstructive pulmonary disease, malignancies, cardiovascular disease, and diabetes mellitus, than younger patients [3]. Indeed, the major causes of death were respiratory involvement (24.2%), malignancies (24.2%), and cardiovascular events (15.6%) in a large Japanese RA cohort [4]. The impairment of hepatic and renal functions, decreased body water and albumin levels, and increased body fat with aging may affect drug pharmacokinetics and pharmacodynamics [5]. The treatment strategy for elderly patients is often influenced by these comorbidities in real-world settings [6], although randomized clinical trials (RCTs) rarely include elderly patients with comorbidities [7]. With aging, both innate and adaptive immune system changes occur, resulting in a break in self-tolerance and proinflammatory promotion (higher circulating levels of tumor necrosis factor [TNF] and interleukin [IL]-6), which is called immunosenescence [8]. Patients with elderly-onset RA are sometimes associated with a higher level of inflammation and risk of rapid joint destruction than those with younger-onset RA [9, 10]. Elderly patients are less likely to achieve remission, and higher baseline disease activity diminishes the clinical response to the treatment [11]. Nevertheless, elderly patients tend to receive less doses and frequency of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate (MTX) and biological DMARDs (bDMARDs), than younger patients [12].

Regarding safety, the risk of infection increases with aging, and RA patients with two or more comorbidities, chronic renal or lung disease, and previous infection are particularly at high risk [13]. RA increases the risk of stroke and myocardial infarction by two-fold and the risk of death from cardiovascular disease by 30% [14]. Moreover, RA is associated with an increased risk of cancer, such as non-Hodgkin's and Hodgkin's lymphoma, non-melanoma skin cancer, and lung cancer [15]. The aim of this report was to review and discuss the recent evidence of the efficacy and safety of bDMARDs and Janus kinase inhibitors (JAKi) in elderly patients with RA.

## Treatment of elderly patients with RA

Glucocorticoid (GC) is more frequently used in elderly patients than in younger patients with RA, although the risk of infection may increase even with low doses (≤5 mg/day prednisolone equivalent) compared with any other csDMARDs or TNF inhibitors (TNFi) [13]. MTX works synergistically with bDMARDs, increasing their efficacy and inhibiting the production of antidrug antibody against bDMARDs. Elderly patients who are tolerant to the MTX+TNFi combination therapy show higher treatment retention than those to the TNFi monotherapy, particularly with infliximab (IFX) and adalimumab (ADA) [16]. However, 30%–50% of patients using MTX experience adverse events that lead to treatment discontinuation, which may increase with aging [17]. In Japan, csDMARDs such as tacrolimus (TAC) and iguratimod (IGU) are also used in combination with bDMARDs in patients who are intolerant to MTX. TAC in a post-marketing surveillance [18] and IGU were both effective in patients who showed an inadequate response to bDMARDs [19, 20].

The European League against Rheumatism (EULAR) announced a 2019 recommendation regarding the management of RA, in which cytotoxic T lymphocyte-associated antigen-4-immunoglobulin (CTLA4-Ig; abatacept [ABT]), anti-interleukin (IL)-6 receptor antibody (tocilizumab [TCZ] and salirumab [SAR]), anti-CD20 antibody (rituximab [RTX]), and JAKi are considered equivalent to TNFi [7]. However, RCTs referred to in the recommendation often recruited younger patients with less comorbidities who are different from those in real-world settings [21], and only 12%–22% patients were elderly in bDMARDs RCTs [22].

Thus, investigating the efficacy and safety of bDMARDs and JAKi in elderly patients with RA is of great interest. Recently, cohort-based observational studies have increasingly been conducted to investigate the performance of bDMARDs [23-25] and JAKi [26-28], and drug retention is considered a major index of both treatment efficacy and safety in real-world settings [26-29].

**Anti-TNF inhibitors in elderly patients with RA**

TNFi were the first bDMARDs used for RA, and evidence has accumulated regarding the efficacy, safety, and retention of the agents, especially in IFX, ADA, and etanercept (ETN) [30-34]. Other TNFi, such as golimumab (GLM) and certolizumab pegol (CZP), were approved lately, and reliable

evidence on these agents in elderly patients was still lacking in previous reviews regarding bDMARDs in elderly patients [1, 35].

**Efficacy**

Previous studies demonstrated that aging is one of the negative predictors of good response [32] and remission [36] of TNFi. TNFi were equally or slightly less effective in decreasing disease activity and improving physical function, particularly in patients aged >75 years [37, 38]. Chronic inflammation may have a negative impact on joint destruction and physical function, and besides aging, disease duration may have a great impact on treatment outcome. Indeed, ETN was equally effective in both younger and elderly populations, although disease duration was associated with lower achievement of ACR50 and ACR70 response and remission [39]. On the other hand, other studies demonstrated that in combination with MTX, TNFi seem to be equally effective in the young, older, and very old populations in terms of both disease activity and radiographic progression [37, 40]. From the post hoc analysis of a post-marketing surveillance in Japan, GLM showed comparable improvements of disease activity between younger (< 75 years) and elderly (≥ 75 years) patients [41]. A recent study also revealed that CZP showed a similar effectiveness and retention between patients with younger- and elderly-onset RA [42].

**Safety and tolerability**

In large Dutch (DREAM) [38] and Swiss (SCQM-RA) [37] cohorts, the drug retention of bDMARDs was similar between the young, older, and very old patients with RA. However, other studies demonstrated that although the efficacy was similar, the discontinuation rates of bDMARDs were higher in elderly patients than in younger patients, mainly owing to adverse events [43, 44]. A meta-analysis revealed that disease duration was associated with higher discontinuation rates of TNFi due to adverse events, although aging did not show a significant correlation [34]. Taken together, prolonged disease duration (sometimes associated with aging) may lead to comorbidities associated with adverse events in TNFi treatment.

Considering the difference between the TNFi, ETN showed higher retention than ADA and IFX in all age groups [30, 34]. GLM tended to show a higher retention rate than other TNFi when matched as per propensity scores in Japanese patients with RA [45], and GLM tended to show higher retention rates due to the lack of effectiveness than other TNFi in elderly patients (aged ≥65 years) [6].

Patients with RA are more susceptible to infection than non-RA patients, and aging was also a significant risk factor of infection [46]. Infection is the most common adverse event associated with the administration of TNFi, which is most frequent in the respiratory tract (such as pneumonia and herpes zoster virus (HZV) infection), and the incidence rate of serious infections was higher in elderly patients with RA [13, 47]. The incidence of serious infection was 20% higher in patients with TNFi than in those without TNFi, especially during the first 6 months [48]. Moreover, the incidence of serious infection was three-fold higher in elderly patients treated with TNFi, especially during the first 3 months [49]. Of note, although TNFi may increase the risk of infection, GC exposure and previous infection are also significant risk factors [13, 50]. Use of GC doubled the incidence rate of serious bacterial infection in patients aged > 65 years, with clear dose-dependent relationships [50]. Although the crude infection rate increased with aging in both the TNFi- and csDMARD-initiated groups, the adjusted hazard ratio was similar between the groups [48].

Aging and GC use are the independent risk factors of HZV infection in patients with RA [51]. The estimated incidence rate of HZV infection in elderly patients with RA who were receiving TNFi was comparable among all the TNFi agents, ranging from 6% to 7% [51, 52]. Regarding tuberculosis (TB), after a screening for past infections, TNFi use seemed to be not associated with increased incidence of TB as compared with the control group or general population [53, 54].

TNF is involved in the development of arteriosclerosis, and patients (aged ≥50 years) treated with TNFi were associated with a 13% reduction in cardiovascular events [55]. On the other hand, patients treated with ABT were at 28% lower risk of acute myocardial infarction than those treated with TNFi (data of ADA, CZP, ETN, GLM, and IFX) [56]. A possible mechanism is that T-cell costimulation by CD28–CD80/CD86 strongly induced the development of atherosclerosis in a mice model, which was inhibited by ABT treatment [57].

TNFi was associated with an increased risk of hospitalization caused by heart failure in elderly patients (hazard ratio, 1.61) [58], although it should be noted that oral GC was an important dose-dependent risk factor of cardiovascular morbidity [55, 56].

RA is associated with a higher risk of certain types of cancer, including lymphoma and non-melanoma skin cancer, although TNFi did not increase the incidence of any type of cancer in both younger and elderly patients with RA [59]. Indeed, the incidence rate of cancer in elderly patients did not differ between the ETN-treated patients and the control group [22]. The risk of toxic adverse events, such as lupus- and vasculitis-like events, which may be associated with the induction of antinuclear antibody production after TNFi treatment, tended to be lowest in CZP among all TNFi [60].

## Non-TNF inhibitors in elderly patients with RA

### Abatacept

Abatacept (ABT) is a cytotoxic T-lymphocyte-associated protein 4-immunoglobulin (CTLA4-Ig) that selectively modulates T-cell costimulation. ABT showed similar treatment response rates (good response and remission) in younger, older (aged 65–74 years), and very old (aged >74 years) patients in the French prospective cohort [61], and the effectiveness of ABT in bDMARDs-naive younger and elderly patients was comparable [62]. In a Medicare dataset-based retrospective study, co-treatment with MTX did not influence the treatment persistence of ABT in elderly patients [16], which indicates the low dependency of ABT on MTX. Considering other factors that affect the effectiveness of ABT, anticyclic citrullinated peptide antibody positivity significantly correlated with sustained clinical remission in elderly patients [62].

Regarding safety, ABT showed a lower risk of hospitalized infection than TNFi [63] or with all other bDMARDs [64]. These results may be partially due to the fact that TNF receptor-1 and IL-6 are associated with innate immune response to bacterial infection [65], although ABT may not affect innate immune response considering its mode of action. However, it should be noted that the risk factors of serious infection associated with ABT therapy were older age and a history of serious infection, which were similar to those of other bDMARDs [66].

Another recent report suggested the effectiveness of ABT in RA-associated interstitial lung disease, although the number of patients was relatively small [67]. This may be partially due to the results that serum titers of second-generation anticyclic citrullinated peptide antibodies (anti-CCP2) are associated with the severity and extent of interstitial lung disease in RA [68], and ABT significantly lowered the serum anti-CCP2 levels at 2.5 years follow-up [69], although further investigation may be required.

The pooled data of ABT showed no significant difference in the incidence of malignancy between ABT and placebo [70]. However, a recent report showed that ABT was significantly associated with an increased risk of melanoma (reporting odds ratio, 1.58) because ABT has an opposite action on CTLA-4 antibody (ipilimumab), which is used for the treatment of melanoma [71]. In addition, concerns in vaccination have been raised during ABT treatment because ABT with csDMARDs reduced the response to the pneumococcal pneumoniae [72] and influenza vaccines [73].

Taken together, ABT showed the lowest discontinuation rate due to lack of effectiveness and the toxic adverse events among seven bDMARDs in elderly patients with RA (aged ≥65 years) [6], which may suggest a high total retention of ABT in elderly patients.

**Anti-IL-6 agents**

TCZ is a humanized and SAR is a human monoclonal antibody against the IL-6 receptor. IL-6 is involved in various pathophysiologies of RA such as C-reactive protein (CRP) production from hepatocyte, immunoglobulin production from B cells, and osteoclast activation [74]. In fact, patients with elderly-onset RA showed higher serum IL-6 and CRP levels than those with younger-onset RA [9]. In addition, patients treated with TCZ showed a relatively low rate of antidrug antibody production (0.7%–2.0%) irrespective of the combination of csDMARDs, which suggests its low immunogenicity [75]. Taken together, blocking IL-6 signaling in elderly patients with RA may provide theoretical advantages, particularly in those who are not tolerant to MTX.

Younger age was a predictor of good EULAR response of TCZ [76], and elderly patients showed a lower and good EULAR response than younger patients (40.1% vs. 61.0%), although the treatment retention rates were similar [77]. In addition, TCZ and ABT showed similar good retention rates due

to their effectiveness in elderly (age ≥65 years) patients with RA [6]. Taken together, the effectiveness of TCZ in elderly patients may be similar or slightly diminished by aging but may not lead to treatment discontinuation.

Regarding safety in elderly patients, the most common adverse events of TCZ are infections and allergic reactions [77], although the overall risk of severe infections seems comparable with those of other bDMARDs (most frequent infections were pneumonia and HZV infection) [77, 78]. Lipid changes, including increased serum triglyceride and cholesterol levels, involved in TCZ treatment were not associated with an increased risk of coronary heart disease [79].

TCZ and TNFi showed similar discontinuation rates due to toxic adverse events, although significantly higher than that of ABT in elderly patients with RA [6]. Another recent study that compared TNFi, ABT, and TCZ demonstrated that the drug retention rate was maximal for TCZ in patients aged <75 years but was similar between ABT and TCZ in patients aged ≥75 years [80].

On the other hand, the efficacy and safety of SAR in elderly patients is still unclear. A recent report of the ASCERTAIN study demonstrated no clinically meaningful differences in both safety and laboratory changes between patients treated with SAR and those treated with TCZ (mean age, 52–55 years) [81]. In addition, switching intravenous TCZ to SAR sustained both clinical efficacy and safety [82]. From the results of previous studies, SAR may exhibit similar clinical effectiveness and safety as TCZ in relatively younger populations. However, in phase III randomized, controlled studies of SAR, adverse events, including serious infections, tended to be more frequent in patients aged ≥65 years [83], although further investigation may be required.

**Rituximab**

Rituximab (RTX) is an anti-CD20 monoclonal antibody that targets the surface protein CD20 of B cells. It depletes both normal and pathogenic B cells while maintaining plasma cells and the hematopoietic stem cells, which do not express the CD20 surface antigen. Regarding efficacy, a multicenter prospective study (n = 2,484) demonstrated that the improvement of DAS28 score by RTX was similar between patients aged 40–59 years and >60 years [84]. By contrast, another registry study (n = 1,709) showed that the improvement of DAS28 score was significantly inferior in patients

aged >75 years than patients aged <50 years [85]. Regarding safety, a German cohort study showed that serious adverse events were similar between patients aged <40 years (2.5%) and patients aged >60 years (3.2%) [84]. Another French study revealed that severe infections were more frequent in patients aged 65–74 years (19.5 %) and >75 years (26.5%) than in patients aged <50 years (5%) [85]. No apparent risk was observed in cardiovascular events and malignancy during long-term RTX treatment (11 years) [86]. Taken together, RTX may be similarly or less effective and safe, particularly in very old patients (aged >75 years) compared with younger patients.

**JAK inhibitors**

Regarding efficacy, baricitinib (BAR; JAK1 and JAK2 inhibitor) showed a similar efficacy (ACR 20/50/70 achievement or CDAI/SDAI low disease activity and remission achievement) between young (aged <50 years) and old patients (aged ≥65 years) in the RA-BUILD and RA-BEAM study [87]. In addition, in phase III and long-term extension studies, tofacitinib (TOF; JAK1 and JAK3 inhibitor) showed similar probabilities of ACR20 and ACR50 responses in both younger (aged <65 years) and elderly patients (aged ≥65 years) [88].

In the safety of BAR, elderly patients (aged ≥65 years) tended to show a higher rate of discontinuation because of adverse events (8.8%) than younger patients (aged <50 years; 2.3%), but the rates were similar to those in the age-matched placebo group [87]. Similarly, in TOF treatment, elderly patients (aged ≥65 years) were at a higher risk of adverse events and discontinuation due to comorbidities than younger patients (aged <65 years) [88]. In detail, higher age was associated with an increased risk of HZV [89], major adverse cardiovascular events [90], and gastrointestinal perforation [91] in TOF treatment. From the pooled safety data of the phase II/III studies of peficitinib (PEF; pan-JAK inhibitor), the incidence of serious infection, HZV, and malignancy tended to be higher in patients aged ≥65 years than in patients aged <65 years [92]. However, a recent network meta-analysis revealed that the efficacy and safety of PEF were comparable with those of TOF and BAR in all patient age groups [93]. The data of upadacitinib (JAK1 inhibitor) and filgotinib (JAK1 inhibitor) in elderly patients are still limited to conference presentations, and further investigations may be required. Together, the efficacy of JAKi may be similar between elderly and younger patients,

although the safety of JAKi may be attenuated by aging or aging-related factors. Recently, the safety of the zoster recombinant vaccine in patients with RA has been reported [94], which may be considered in the JAKi treatment of elderly patients. The differences in efficacy and safety by JAK-inhibition selectivity has not been clarified to date.

**Summary of the Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort studies regarding elderly patients with RA**

The ANSWER cohort is an observational multicenter registry of patients with RA in the Kansai district of Japan. Data were retrospectively collected from patients who were examined at seven major university-related hospitals (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medial University, and Osaka Red Cross Hospital).

1) The drug retention of bDMARDs in elderly populations [6]

- A total of 1,098 treatment courses of 661 elderly patients with RAs (aged ≥65 years).
- The treatment courses included abatacept (ABT; n = 272), tocilizumab (TCZ; n = 234), etanercept (ETN; n = 184), golimumab (GLM; n = 159), infliximab (IFX; n = 101), adalimumab (ADA; n = 97), and certolizumab pegol (CZP; n = 51).
- Drug retention rates were estimated at 36 months using the Kaplan–Meier method and adjusted for potential clinical confounders (age, sex, disease duration, concomitant GC and MTX, start date, and the number of switched bDMARDs).
- The drug retention rates for the reasons of discontinuation were as follows: lack of effectiveness [from 55.4% (ETN) to 81.6% (ABT); with significant differences between the groups (Cox P < 0.001)] and toxic adverse events [from 79.3% (IFX) to 95.4% (ABT), Cox P = 0.043].

2) The efficacy and safety of bDMARDs between the elderly-onset RA (EORA) and young-onset RA (YORA) patients [29]

- Among 989 bDMARDs initiators, 364 were in the EORA group (aged ≥60 years) and 625 were in the YORA group (aged <60 years).

- After propensity score matching for confounding factors, generalized estimation equations were used to assess the relationship between the age at RA onset and the clinical effectiveness of bDMARDs at 48 weeks.
- The improvements in clinical disease, drug retention, and discontinuation because of adverse events were similar between the EORA and YORA groups.

**Conclusion**

Elderly patients with RA frequently experience high disease activity and functional disability, which are associated with comorbidities such as renal disfunction, pulmonary disease, and cardiovascular disease. These may prevent them from receiving thorough treatments to achieve remission. In general, bDMARDs tend to show similar retention rates between younger and elderly patients, although elderly patients appear to have a slightly diminished treatment response (probably because of intolerance to csDMARDs such as MTX) and higher serious infection rate (particularly in patients with longer disease duration and very old age or those receiving oral GC). Recent observational cohort studies showed that the drug retention of bDMARDs might have some differences between targeted molecules in elderly patients. Regarding JAKi, the efficacy appears to be similar, although safety (particularly for serious infections, including HZV) may be attenuated by aging. The differences in efficacy and safety by JAK-inhibition selectivity have not been clarified to date. After the careful consideration of comorbidities, the tolerance for csDMARDs, and the balance of risk and benefit, an appropriate choice of bDMARDs or JAKi by each patient's background may be beneficial in the treatment of elderly patients who are difficult to treat with GC or csDMARDs. When the disease activity has improved, a careful dose reduction of combined GC or csDMARDs as well as tapering or spacing of bDMARDs or JAKi may contribute to sustained safety. In addition, the comparison of the efficacy and safety between bDMARDs and JAKi in elderly patients (particularly in long-term treatment) is of great interest and should be clarified in future studies.

**Acknowledgments**

The author thanks all the medical staff for their excellent cooperation in writing this manuscript.

## Conflict of interest

KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University Graduate School of Medicine, which is supported by Taisho. KE has received research grants from Abbie, Asahi-Kasei, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Ono Pharmaceutical, Teijin Pharma, and UCB Japan. KE has received payments for lectures from Abbie, Asahi-Kasei, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Janssen, Mitsubishi-Tanabe, Ono Pharmaceutical, Pfizer, Sanofi, and UCB Japan. KE is a director of the ANSWER Cohort, which was supported by grants from 10 pharmaceutical companies (AbbVie GK, Asahi-Kasei, Ayumi, Chugai, Eisai, Janssen K.K, Ono, Sanofi K.K, Teijin Healthcare, and UCB Japan) and an information technology service company (CAC). These companies had no roles in writing this manuscript.

## References


1. Ishchenko A, Lories RJ. Safety and Efficacy of Biological Disease-Modifying Antirheumatic Drugs in Older Rheumatoid Arthritis Patients: Staying the Distance. Drugs Aging. 2016; 33(6): 387-98.

2. Kato E, Sawada T, Tahara K, Hayashi H, Tago M, Mori H, et al. The age at onset of rheumatoid arthritis is increasing in Japan: a nationwide database study. Int J Rheum Dis. 2017; 20(7): 839-45.

3. Curtis JR, Yang S, Patkar NM, Chen L, Singh JA, Cannon GW, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014; 66(7): 990-7.

4. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol. 2010; 39(5): 360-7.

5. Ranganath VK, Furst DE. Disease-modifying antirheumatic drug use in the elderly rheumatoid arthritis patient. Rheum Dis Clin North Am. 2007; 33(1): 197-217.

6. Ebina K, Hashimoto M, Yamamoto W, Hirano T, Hara R, Katayama M, et al. Drug tolerability and reasons for discontinuation of seven biologics in elderly patients with rheumatoid arthritis -The ANSWER cohort study. PLoS One. 2019; 14(5): e0216624.

7. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020; 79(6): 685-99.

8. Lindstrom TM, Robinson WH. Rheumatoid arthritis: a role for immunosenescence? J Am Geriatr Soc. 2010; 58(8): 1565-75.

9. Chen DY, Hsieh TY, Chen YM, Hsieh CW, Lan JL, Lin FJ. Proinflammatory cytokine profiles of patients with elderly-onset rheumatoid arthritis: a comparison with younger-onset disease. Gerontology. 2009; 55(3): 250-8.

10. Murata K, Ito H, Hashimoto M, Nishitani K, Murakami K, Tanaka M, et al. Elderly onset of early rheumatoid arthritis is a risk factor for bone erosions, refractory to treatment: KURAMA cohort. Int J Rheum Dis. 2018.

11. Arnold MB, Bykerk VP, Boire G, Haraoui BP, Hitchon C, Thorne C, et al. Are there differences between young- and older-onset early inflammatory arthritis and do these impact outcomes? An analysis from the CATCH cohort. Rheumatology (Oxford). 2014; 53(6): 1075-86.

12. Tutuncu Z, Reed G, Kremer J, Kavanaugh A. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis. 2006; 65(9): 1226-9.

13. Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, et al. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013; 65(3): 353-61.

14. Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis. 2006; 65(12): 1608-12.

15. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015; 17: 212.

16. Zhang J, Xie F, Delzell E, Yun H, Lewis JD, Haynes K, et al. Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2015; 67(5): 624-32.

17. Harrison MJ, Kim CA, Silverberg M, Paget SA. Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis? J Rheumatol. 2005; 32(7): 1243-8.

18. Ishida K, Shiraki K, Yoshiyasu T. Evaluation of the Safety and Effectiveness of Add-On Tacrolimus in Patients with Rheumatoid Arthritis Who Failed to Show an Adequate Response to Biological DMARDs: The Interim Results of a Specific Drug Use-Results Survey of Tacrolimus. Drugs R D. 2015; 15(4): 307-17.

19. Ebina K, Miyama A, Tsuboi H, Kaneshiro S, Nishikawa M, Owaki H, et al. The add-on effectiveness and safety of iguratimod in patients with rheumatoid arthritis who showed an inadequate response to tocilizumab. Mod Rheumatol. 2018: 1-8.

20. Yoshikawa A, Yoshida S, Kimura Y, Tokai N, Fujiki Y, Kotani T, et al. Add-on iguratimod as a therapeutic strategy to achieve remission in patients with rheumatoid arthritis inadequately responding to biological DMARDs: A retrospective study. Mod Rheumatol. 2017: 1-8.

21. Wolfe F, Michaud K, Dewitt EM. Why results of clinical trials and observational studies of antitumour necrosis factor (anti-TNF) therapy differ: methodological and interpretive issues. Ann Rheum Dis. 2004; 63 Suppl 2: ii13-ii7.

22. Bathon JM, Fleischmann RM, Van der Heijde D, Tesser JR, Peloso PM, Chon Y, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006; 33(2): 234-43.

23. Ebina K, Hashimoto M, Yamamoto W, Hirano T, Hara R, Katayama M, et al. Drug tolerability and reasons for discontinuation of seven biologics in 4466 treatment courses of rheumatoid arthritis-the ANSWER cohort study. Arthritis Res Ther. 2019; 21(1): 91.

24. Ebina K, Hashimoto M, Yamamoto W, Ohnishi A, Kabata D, Hirano T, et al. Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis -The ANSWER cohort study. PLoS One. 2018; 13(3): e0194130.

25. Hashimoto M, Furu M, Yamamoto W, Fujimura T, Hara R, Katayama M, et al. Factors associated with the achievement of biological disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: the ANSWER cohort study. Arthritis Res Ther. 2018; 20(1): 165.

26. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Drug retention of sarilumab, baricitinib, and tofacitinib in patients with rheumatoid arthritis: the ANSWER cohort study. Clin Rheumatol. 2021.

27. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Drug retention of secondary biologics or JAK inhibitors after tocilizumab or abatacept failure as first biologics in patients with rheumatoid arthritis -the ANSWER cohort study. Clin Rheumatol. 2020; 39(9): 2563-72.

28. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Drug retention of 7 biologics and tofacitinib in biologics-naive and biologics-switched patients with rheumatoid arthritis: the ANSWER cohort study. Arthritis Res Ther. 2020; 22(1): 142.

29. Jinno S, Onishi A, Dubreuil M, Akashi K, Hashimoto M, Yamamoto W, et al. Comparison of the efficacy and safety of biologic agents between elderly-onset and young-onset RA patients: the ANSWER cohort study. Rheumatol Int. 2020; 40(12): 1987-95.

30. Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum. 2009; 61(5): 560-8.

31. Favalli EG, Pregnolato F, Biggioggero M, Becciolini A, Penatti AE, Marchesoni A, et al. Twelve-Year Retention Rate of First-Line Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: Real-Life Data From a Local Registry. Arthritis Care Res (Hoboken). 2016; 68(4): 432-9.

32. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010; 62(1): 22-32.

33. Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis. 2015; 74(2): 354-60.

34. Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford). 2016; 55(3): 523-34.

35. Sugihara T, Harigai M. Targeting Low Disease Activity in Elderly-Onset Rheumatoid Arthritis: Current and Future Roles of Biological Disease-Modifying Antirheumatic Drugs. Drugs Aging. 2016; 33(2): 97-107.

36. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology (Oxford). 2013; 52(10): 1809-17.

37. Genevay S, Finckh A, Ciurea A, Chamot AM, Kyburz D, Gabay C. Tolerance and effectiveness of anti-tumor necrosis factor alpha therapies in elderly patients with rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007; 57(4): 679-85.

38. Radovits BJ, Kievit W, Fransen J, van de Laar MA, Jansen TL, van Riel PL, et al. Influence of age on the outcome of antitumour necrosis factor alpha therapy in rheumatoid arthritis. Ann Rheum Dis. 2009; 68(9): 1470-3.

39. Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011; 63(3): 373-82.

40. Koller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford). 2009; 48(12): 1575-80.

41. Okazaki M, Kobayashi H, Ishii Y, Kanbori M, Yajima T. Real-World Treatment Patterns for Golimumab and Concomitant Medications in Japanese Rheumatoid Arthritis Patients. Rheumatol Ther. 2018; 5(1): 185-201.

42. Torrente-Segarra V, Fernandez Prada M, Exposito Moliner R, Garrido Punal NP, Sanchez-Andrade Fernandez A, Lamua Riazuelo JR, et al. How elderly rheumatoid arthritis patients respond at one year of treatment with certolizumab pegol. Rheumatol Int. 2019; 39(2): 395-8.

43. Filippini M, Bazzani C, Favalli EG, Marchesoni A, Atzeni F, Sarzi-Puttini P, et al. Efficacy and safety of anti-tumour necrosis factor in elderly patients with rheumatoid arthritis: an observational study. Clin Rev Allergy Immunol. 2010; 38(2-3): 90-6.

44. Majithia V, Peel C, Geraci SA. Rheumatoid arthritis in elderly patients. Geriatrics. 2009; 64(9): 22-8.

45. Sruamsiri R, Kameda H, Mahlich J. Persistence with Biological Disease-modifying Antirheumatic Drugs and Its Associated Resource Utilization and Costs. Drugs Real World Outcomes. 2018; 5(3): 169-79.

46. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002; 46(9): 2287-93.

47. Fleischmann R, Iqbal I. Risk: benefit profile of etanercept in elderly patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. Drugs Aging. 2007; 24(3): 239-54.

48. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011; 50(1): 124-31.

49. Toh S, Li L, Harrold LR, Bayliss EA, Curtis JR, Liu L, et al. Comparative safety of infliximab and etanercept on the risk of serious infections: does the association vary by patient characteristics? Pharmacoepidemiol Drug Saf. 2012; 21(5): 524-34.

50. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum. 2007; 56(6): 1754-64.

51. McDonald JR, Zeringue AL, Caplan L, Ranganathan P, Xian H, Burroughs TE, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis. 2009; 48(10): 1364-71.

52. Iwanaga N, Arima K, Terada K, Ueki Y, Horai Y, Suzuki T, et al. Risk factors of adverse events during treatment in elderly patients with rheumatoid arthritis: an observational study. Int J Rheum Dis. 2017; 20(3): 346-52.

53. Cantini F, Niccoli L, Goletti D. Tuberculosis risk in patients treated with non-anti-tumor necrosis factor-alpha (TNF-alpha) targeted biologics and recently licensed TNF-alpha inhibitors: data from clinical trials and national registries. J Rheumatol Suppl. 2014; 91: 56-64.

54. Souto A, Maneiro JR, Salgado E, Carmona L, Gomez-Reino JJ. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. Rheumatology (Oxford). 2014; 53(10): 1872-85.

55. Nurmohamed M, Bao Y, Signorovitch J, Trahey A, Mulani P, Furst DE. Longer durations of antitumour necrosis factor treatment are associated with reduced risk of cardiovascular events in patients with rheumatoid arthritis. RMD Open. 2015; 1(1): e000080.

56. Zhang J, Xie F, Yun H, Chen L, Muntner P, Levitan EB, et al. Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis. Ann Rheum Dis. 2016; 75(10): 1813-8.

57. Ewing MM, Karper JC, Abdul S, de Jong RC, Peters HA, de Vries MR, et al. T-cell co-stimulation by CD28-CD80/86 and its negative regulator CTLA-4 strongly influence accelerated atherosclerosis development. Int J Cardiol. 2013; 168(3): 1965-74.

58. Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J. 2008; 156(2): 336-41.

59. Haynes K, Beukelman T, Curtis JR, Newcomb C, Herrinton LJ, Graham DJ, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum. 2013; 65(1): 48-58.

60. Jani M, Dixon WG, Kersley-Fleet L, Bruce IN, Chinoy H, Barton A, et al. Drug-specific risk and characteristics of lupus and vasculitis-like events in patients with rheumatoid arthritis treated with TNFi: results from BSRBR-RA. RMD Open. 2017; 3(1): e000314.

61. Lahaye C, Soubrier M, Mulliez A, Bardin T, Cantagrel A, Combe B, et al. Effectiveness and safety of abatacept in elderly patients with rheumatoid arthritis enrolled in the French Society of Rheumatology's ORA registry. Rheumatology (Oxford). 2016; 55(5): 874-82.

62. Sekiguchi M, Fujii T, Matsui K, Murakami K, Morita S, Ohmura K, et al. Differences in Predictive Factors for Sustained Clinical Remission with Abatacept Between Younger and Elderly Patients with Biologic-naive Rheumatoid Arthritis: Results from the ABROAD Study. J Rheumatol. 2016; 43(11): 1974-83.

63. Chen SK, Liao KP, Liu J, Kim SC. Risk of Hospitalized Infection and Initiation of Abatacept versus TNF Inhibitors among Patients with Rheumatoid Arthritis: a Propensity Score-Matched Cohort Study. Arthritis Care Res (Hoboken). 2018.

64. Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD, et al. Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. Arthritis Rheumatol. 2016; 68(1): 56-66.

65. Albrecht LJ, Tauber SC, Merres J, Kress E, Stope MB, Jansen S, et al. Lack of Proinflammatory Cytokine Interleukin-6 or Tumor Necrosis Factor Receptor-1 Results in a Failure of the Innate Immune Response after Bacterial Meningitis. Mediators Inflamm. 2016; 2016: 7678542.

66. Salmon JH, Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, et al. Predictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia and Rheumatoid Arthritis (ORA) registry. Ann Rheum Dis. 2016; 75(6): 1108-13.

67. Fernandez-Diaz C, Loricera J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum. 2018; 48(1): 22-7.

68. Rocha-Munoz AD, Ponce-Guarneros M, Gamez-Nava JI, Olivas-Flores EM, Mejia M, Juarez-Contreras P, et al. Anti-Cyclic Citrullinated Peptide Antibodies and Severity of Interstitial Lung Disease in Women with Rheumatoid Arthritis. J Immunol Res. 2015; 2015: 151626.

69. Wunderlich C, Oliviera I, Figueiredo CP, Rech J, Schett G. Effects of DMARDs on citrullinated peptide autoantibody levels in RA patients-A longitudinal analysis. Semin Arthritis Rheum. 2017; 46(6): 709-14.

70. Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. J Rheumatol. 2013; 40(6): 787-97.

71. de Germay S, Bagheri H, Despas F, Rousseau V, Montastruc F. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study. Rheumatology (Oxford). 2020; 59(9): 2360-7.

72. Migita K, Akeda Y, Akazawa M, Tohma S, Hirano F, Ideguchi H, et al. Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. Arthritis Res Ther. 2015; 17: 357.

73. Ribeiro AC, Laurindo IM, Guedes LK, Saad CG, Moraes JC, Silva CA, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013; 65(3): 476-80.

74. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. Am J Health Syst Pharm. 2008; 65(15): 1413-8.

75. Burmester GR, Choy E, Kivitz A, Ogata A, Bao M, Nomura A, et al. Low immunogenicity of tocilizumab in patients with rheumatoid arthritis. Ann Rheum Dis. 2017; 76(6): 1078-85.

76. Yamanaka H, Tanaka Y, Inoue E, Hoshi D, Momohara S, Hanami K, et al. Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol. 2011; 21(2): 122-33.

77. Pers YM, Schaub R, Constant E, Lambert J, Godfrin-Valnet M, Fortunet C, et al. Efficacy and safety of tocilizumab in elderly patients with rheumatoid arthritis. Joint Bone Spine. 2015; 82(1): 25-30.

78. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res (Hoboken). 2015; 67(5): 731-6.

79. Strang AC, Bisoendial RJ, Kootte RS, Schulte DM, Dallinga-Thie GM, Levels JH, et al. Pro-atherogenic lipid changes and decreased hepatic LDL receptor expression by tocilizumab in rheumatoid arthritis. Atherosclerosis. 2013; 229(1): 174-81.

80. Kawabe A, Nakano K, Kubo S, Asakawa T, Tanaka Y. Differential long-term retention of biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis by age group from the FIRST registry. Arthritis Res Ther. 2020; 22(1): 136.

81. Emery P, Rondon J, Parrino J, Lin Y, Pena-Rossi C, van Hoogstraten H, et al. Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2019; 58(5): 849-58.

82. Emery P, van Hoogstraten H, Thangavelu K, Mangan E, St John G, Verschueren P. Subcutaneous Sarilumab in Patients With Rheumatoid Arthritis who Previously Received Subcutaneous Sarilumab or Intravenous Tocilizumab: An Open-Label Extension of a Randomized Clinical Trial. ACR Open Rheumatol. 2020; 2(11): 672-80.

83. Genovese MC, Fleischmann R, Kivitz A, Lee EB, van Hoogstraten H, Kimura T, et al. Efficacy and safety of sarilumab in combination with csDMARDs or as monotherapy in subpopulations of patients with moderately to severely active rheumatoid arthritis in three phase III randomized, controlled studies. Arthritis Res Ther. 2020; 22(1): 139.

84. Wendler J, Burmester GR, Sorensen H, Krause A, Richter C, Tony HP, et al. Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. Arthritis Res Ther. 2014; 16(2): R80.

85. Payet S, Soubrier M, Perrodeau E, Bardin T, Cantagrel A, Combe B, et al. Efficacy and safety of rituximab in elderly patients with rheumatoid arthritis enrolled in a French Society of Rheumatology registry. Arthritis Care Res (Hoboken). 2014; 66(9): 1289-95.

86. van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. J Rheumatol. 2015; 42(10): 1761-6.

87. Fleischmann R, Alam J, Arora V, Bradley J, Schlichting DE, Muram D, et al. Safety and efficacy of baricitinib in elderly patients with rheumatoid arthritis. RMD Open. 2017; 3(2): e000546.

88. Curtis JR, Schulze-Koops H, Takiya L, Mebus CA, Terry KK, Biswas P, et al. Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis. Clin Exp Rheumatol. 2017; 35(3): 390-400.

89. Curtis JR, Xie F, Yang S, Bernatsky S, Chen L, Yun H, et al. Risk for Herpes Zoster in Tofacitinib-Treated Rheumatoid Arthritis Patients With and Without Concomitant Methotrexate and Glucocorticoids. Arthritis Care Res (Hoboken). 2019; 71(9): 1249-54.

90. Charles-Schoeman C, DeMasi R, Valdez H, Soma K, Hwang LJ, Boy MG, et al. Risk Factors for Major Adverse Cardiovascular Events in Phase III and Long-Term Extension Studies of Tofacitinib in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2019; 71(9): 1450-9.

91. Xie F, Yun H, Bernatsky S, Curtis JR. Brief Report: Risk of Gastrointestinal Perforation Among Rheumatoid Arthritis Patients Receiving Tofacitinib, Tocilizumab, or Other Biologic Treatments. Arthritis Rheumatol. 2016; 68(11): 2612-7.

92. Takeuchi T, Tanaka Y, Rokuda M, Izutsu H, Kaneko Y, Fukuda M, et al. A pooled safety analysis of peficitinib (ASP015K) in Asian patients with rheumatoid arthritis treated over a median of 2 years. Mod Rheumatol. 2020: 1-13.

93. Tanaka Y, Okumura H, Kim S, Dorey J, Wojciechowski P, Chorazy J, et al. Comparative Efficacy and Safety of Peficitinib Versus Tofacitinib and Baricitinib for Treatment of Rheumatoid Arthritis: A Systematic Review and Network Meta-Analysis. Rheumatol Ther. 2021.

94. Stevens E, Weinblatt ME, Massarotti E, Griffin F, Emani S, Desai S. Safety of the Zoster Vaccine Recombinant Adjuvanted in Rheumatoid Arthritis and Other Systemic Rheumatic Disease Patients: A Single Center's Experience With 400 Patients. ACR Open Rheumatol. 2020; 2(6): 357-61.