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Review Article

Title:

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

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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 (\geq 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-naïve 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 dysfunction, 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.

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Conflict of interest

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