Safety and efficacy of interleukin inhibitors in elderly patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis

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Abstract

Elderly patients with rheumatoid arthritis, psoriasis and psoriatic arthritis encompass those with elderly-onset disease, over 60 years of age, but also those with earlier disease onset who entered old age. Considering the age-related changes of the immune system, possible frailty, susceptibility to infection and concomitant comorbidity that implies multiple medicines, the treatment of these diseases in elderly patients can be challenging. Interleukin inhibitors have been shown to be an efficient and safe treatment for these diseases. However, elderly patients with these diseases were often included in the pivotal clinical trials for interleukin inhibitors in numbers insufficient to determine whether they responded differently from younger subjects. The aim of this paper was to review the findings on the efficacy and safety of interleukin inhibitor treatment in elderly patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis. The findings suggest that, for all the interleukin inhibitors reviewed herein, used in elderly patients with rheumatoid arthritis, or with psoriasis and psoriatic arthritis, the efficacy was comparable to younger patients. Furthermore, the incidence of reported adverse events was similar in these two age groups. Severe adverse events, which were related to sarilumab treatment for rheumatoid arthritis and secukinumab treatment for psoriasis, were higher in elderly patients. The reviewed findings suggest that the interleukin inhibitors approved and currently in use in clinical practice for the treatment of rheumatoid arthritis, psoriasis, and psoriatic arthritis can be considered a safe and efficient option for these diseases in elderly patients.

Key words: interleukin inhibitors, elderly patients, safety, efficacy

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Introduction

Prolonged human life expectancy and global decline in fertility rates have led to an increase in the age of the population in almost all regions of the world (1). The United Nations demographic projections from 2019 indicate that the number of people over the age of 65 will have doubled by 2050 (1). Along with the extension of the human lifespan, the need for the society to provide adequate care for the elderly with health problems is growing.

Rheumatoid arthritis and psoriasis are among the most prevalent chronic inflammatory diseases (2-4). An inflammatory process in rheumatoid arthritis primarily affects the joints (2,5). A multisystem inflammation present in psoriasis predominantly affects the skin and joints (6,7). Psoriatic arthritis is present in 6-42% of patients with psoriasis (3,8-11).

Elderly patients with rheumatoid arthritis may be those with a late-onset rheumatoid arthritis and those in whom the disease started at an earlier age and lasted until old age. The prevalence of rheumatoid arthritis in elderly population (≥60 years) is approximately 2% (12). Late- or elderly-onset rheumatoid arthritis refers to the disease onset at age 60 or over and represents 10-33% of all cases of rheumatoid arthritis (13). A comparison of disease treatment in patients with elderly-onset and younger-onset rheumatoid arthritis, using the Consortium of Rheumatology Researchers of North America registry, revealed that patients with elderly-onset receive biological agents considerably less frequently than those with younger-onset rheumatoid arthritis, although no difference between disease duration, activity and severity was detected (14). Other studies also suggest that, even though elderly patients with rheumatoid arthritis have similar or greater disease activity compared to that present in younger patients, they do not receive the same treatment as younger patients with rheumatoid arthritis (15-20). It should be noted that, in addition to the observed clinical and laboratory differences between elderly-onset and younger-onset rheumatoid arthritis (15,16,21), higher synovial fluid levels of interleukin (IL)-6 were detected in patients with elderly-onset rheumatoid arthritis than in those with younger onset (21). The use of multiple drugs seems to be more common and considerable among elderly patients with rheumatoid arthritis and patients with longer disease duration, most likely due to the developed comorbidities (22). Furthermore, it has been shown that age represents an important influencing factor for rheumatologists’ decision to escalate care, such as the introduction of a new biological drug into therapy, in patients with rheumatoid arthritis (23).

One-quarter of psoriasis patients are those with late-onset psoriasis, that is, with the onset of the disease at or after the age of 40, with a peak between 57 and 60 years of age (24,25). A difference in genetic background has been reported among psoriasis patients with early- and late-onset psoriasis (25,26). It has been suggested that polymorphism at the IL-1B gene is significantly associated with late-onset, but not early-onset psoriasis (27). Furthermore, studies of psoriasis occurring over the age of 60, that is, elderly-onset psoriasis, report differences in clinical patterns and pathogenesis in comparison with
psoriasis with earlier onset (28,29). Also, given the frequently present comorbidity in elderly psoriasis patients, taking some drugs (lithium, synthetic antimalarial drugs, nonsteroidal anti-inflammatory drugs, tetracyclines, interferons, terbinafine, etc.) can exacerbate pre-existing psoriatic lesions or induce new lesions (30,31).

As for psoriatic arthritis, elderly patients encompass those with elderly-onset psoriatic arthritis (>60 years), but also those with earlier disease onset who entered old age (32,33). A more severe onset of psoriatic arthritis was reported in patients with elderly-onset than in patients with younger-onset psoriatic arthritis, as demonstrated by a greater number of active joints, foot bone erosions and greater inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate (32). Furthermore, a more evident disease progression and activity and worse functional outcome were found in psoriatic arthritis patients with elderly onset than in those with younger onset (32,33). A more severe onset and poorer outcome in patients with elderly-onset psoriatic arthritis may be associated with higher concentrations of IL-1β and IL-6 found in the synovial fluid of the affected knees in elderly-onset patients, compared to the concentrations of these interleukins in the synovial fluid of the same affected joints in younger-onset psoriatic arthritis patients (32).

Targeting interleukins, a type of cytokine that binds to its receptor on target cells and influences immune response (34), has proved to be beneficial in various diseases, including rheumatoid arthritis (IL-10, IL-11, anti-IL-1, anti-IL-6) and psoriasis (IL-10, IL-11, anti-IL-12, anti-IL-23, anti-IL-17) (35-37). Pharmacotherapy research in elderly population is challenging. The measurement of outcomes, analytical plan and study implementation issues are stumbling blocks in obtaining relevant data in drug efficacy and safety studies in the geriatric population (38). Aging is a complex process that involves alterations in physical, psychological, and social factors. The implications of these changes are numerous and diverse, and may affect susceptibility to disease, its clinical and laboratory manifestations, but also, efficacy, tolerability, and safety of therapy (39). Moreover, these age-related changes may generate obstacles for the enrollment of elderly in clinical trials, especially the frail ones, and for conducting controlled trial in elderly population. Namely, limited cognitive and physical reserve, communication issues (hearing or vision difficulties), multiple comorbidities, polypharmacy, increased susceptibility to infection, medication nonadherence are just some of the challenges of conducting a clinical trial in elderly population (38,40-42). However, except patient-related barriers to enrollment of elderly subjects in a clinical trial of a novel treatment, physician- and trial-related barriers have also been identified, but possible solutions for these issues have been suggested as well (40,41). Although the elderly patients were included in the pivotal clinical trials for interleukin inhibitors reviewed here, the number of subjects aged 65 years and older was often not sufficient to determine whether they responded differently from younger subjects (43-48).

Age-related physiological and functional alterations cause changes in the pharmacokinetics and pharmacodynamics of drugs (49,50). Pharmacodynamics has been less studied than pharmacokinetics in geriatric population (50), and data on
pharmacodynamic properties of interleukin inhibitors in geriatric population are scarce. Also, it should be borne in mind that biologics often exhibit unique pharmacokinetic and pharmacodynamic properties, which are different from those of small-molecule drugs (51), and that if monoclonal antibodies are considered, such properties depend on monoclonal antibody structure and target antigen (52).

This review focuses on the effectiveness and safety of interleukin inhibitors used in elderly patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis.

**Regulatory framework for the enrollment of geriatric subjects in clinical trials**

The guideline entitled: “ICH E7 Studies in support of special populations: geriatrics” (published in 1994), that addresses clinical evaluation of medicinal products in geriatric population, was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (53). The ICH E7 guideline was revised, resulting in an addendum, published in 2010, that answered questions addressed in the note for guidance on ICH E7 (54). These guidelines recommended that *drugs should be studied in all age groups, including elderly, and that the population enrolled in clinical trials should be representative of the target patient population*. The addendum to ICH E7 advocates the enrollment of *more than 100 geriatric patients in the Phase 2 and 3 databases*, for drugs used in diseases not unique to, but present in the elderly, and that *in the marketing application, data should be presented for various age groups (for example <65, 65-74, 75-84 and >85)* (54). Furthermore, the European Medicines Agency (EMA) published the Geriatric Medicines Strategy in 2011 and established the Geriatric Expert Group to assist in the implementation of this strategy (55,56). The Geriatric Expert Group performed an analysis of the available instruments/methods for the characterization of frailty status and the result of this work was *Points to consider on frailty: Evaluation instruments for baseline characterization of clinical trial populations* (57).

**Age-related changes of interleukins**

Monoclonal antibodies target those components of the immune system whose dysregulation has occurred within a specific disorder. However, the biological process of aging itself brings various alterations to the immune system that affect both its innate and acquired compartments (58,59,60). The entire immune system, including immune cells, lymphoid organs, and soluble molecules, is affected by aging (58,61). These changes do not necessarily result in reduced functions of the immune system, but, more precisely, in their modification (61,62). Chronic, low-grade inflammation, which develops with aging, involves elevated circulating levels of IL-1, IL-6, and tumor necrosis factor (TNF)-α (63,64,65). In addition to the reported positive correlation between IL-6 plasma levels and age (65), IL-6 has been recognized as an important predictor of adverse outcomes and mortality in the elderly population (66). It has been shown that the frequency of T helper (Th) 17 cells, major source of IL-17 (67), was lower in peripheral blood of
healthy elderly subjects (≥65 years) than in younger subjects (≤40 years), probably due to a decreased frequency of Th17 cells among memory CD4+ T cells (68). Also, the production of IL-17 by the stimulated T cells was significantly lower for healthy old than young men (69). In subjects over 75 years, poor nutritional status and frailty were associated with decreased IL-12p70 and IL-23 production (70).

**Pharmacokinetic and pharmacodynamic interactions of interleukin inhibitors with pharmacological treatment of comorbid diseases in elderly patients**

Coexisting chronic disease/s can affect the clinical course of the primary disease, as well as the safety and efficacy of the applied therapy. Two or more chronic diseases are often present in the elderly (71,72). Almost half of the elderly population (≥65 years) in the United States have three or more chronic diseases (72). The leading chronic conditions are cardiovascular diseases, chronic respiratory diseases, metabolic syndrome, and tumors (71,72). The most significant common risk factors for these disorders are smoking and obesity, which are also associated with low-grade, chronic inflammation (73,74). Furthermore, the elderly population use almost one-third of all drugs (75).

Considering that the disposition of interleukin inhibitors, which are monoclonal antibodies, is not mediated by any of the microsomal cytochrome (CYP) P450 enzymes or chemical drug transporters, no direct competition of interleukin inhibitors and small molecule drugs would be expected when co-administered (76). Nevertheless, monoclonal antibodies, that specifically block cytokines may exhibit an indirect effect on drug metabolism in liver. More precisely, it has been demonstrated that certain cytokines inhibit CYP450 enzymes, but also have an impact on the expression of transporters of small molecule drugs (76,77). Proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, have been observed to downregulate CYP450 enzymes in hepatocytes (78), presumably via NO synthesis (79). Accordingly, tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody that hinders IL-6 binding to its receptor (80), increased CYP3A4 activity in patients with rheumatoid arthritis (81). Consequently, plasma levels of simvastatin (CYP3A4 substrate) in patients with rheumatoid arthritis, previously augmented due to IL-6 induced inhibition of CYP3A4, were reduced to levels detected in healthy individuals one week after tocilizumab infusion (81). Also, tocilizumab enhances the clearance of CYP1A2 and 2C9 substrates (76). On the other hand, the clearance of monoclonal antibodies may be affected by immunosuppressive medications, such as methotrexate, azathioprine and mercaptopurine, presumably by reducing the synthesis of immunoglobulin G antibodies against these therapeutic monoclonal antibodies (82,83). Finally, altering the expression of the target molecule of monoclonal antibody is also a way in which small molecule drugs can influence the clearance of monoclonal antibodies (76). Overall, the development of an adequate therapeutic approach in the treatment of elderly patients with complex comorbidity requires consideration of potential monoclonal antibodies - small molecule drug interactions.
Elderly patients with rheumatoid arthritis or psoriasis are often undertreated (14,42), and this is partly due to physician reluctance to include biological treatment (20). The causes underlying this avoidance are a lack of data, concerns about adverse effects, multiple comorbidities, possible interactions with other drugs or poor adherence in elderly patients. Given that clinical trials of biological drugs often involve elderly patients, especially those with comorbidities present, in numbers insufficient to derive relevant conclusions, and that elderly patients are the majority users of many drugs treating chronic conditions, it is crucial to conduct clinical trials to evaluate the efficacy and safety of biological drugs in the population of elderly patients.

**Efficacy and safety of interleukin inhibitors in elderly patients with rheumatoid arthritis**

Interleukin inhibitors, which act as antagonists of IL-6 receptor, tocilizumab and sarilumab, were approved for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) (84-87). Sirukumab, human monoclonal antibody, that selectively blocks circulating IL-6 was rejected for approval by the US Food and Drug Administration (FDA), due to uncertainty regarding the safety profile (88). Anakinra, a recombinant form of naturally occurring IL-1 receptor antagonist, which binds to the IL-1 type I receptor, antagonizing the effects of both IL-1α and IL-1β (89,90), was approved by FDA in 2001 (91), but wasn’t included in the 2015 American College of Rheumatology (ACR) guideline for the treatment of rheumatoid arthritis, due to its infrequent use in rheumatoid arthritis and lack of new data since 2012 (92). Also, anakinra is not included in the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update (93).

Tocilizumab, a humanized anti-human IL-6 receptor monoclonal antibody, inhibits IL-6 signaling through both soluble and membrane-bound IL-6 receptors (94). In addition to the abovementioned indication, in the European Union (EU) tocilizumab can be used in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate (95,96). In patients with rheumatoid arthritis tocilizumab is administered intravenously or subcutaneously, at a recommended (in the EU) dose of 8 mg/kg body weight, given once every four weeks or 162 mg once weekly, respectively (95,96). Pers et al. (2015) compared the efficacy and safety of tocilizumab in patients with rheumatoid arthritis in two age groups, over 65 years (n=61), and under 65 years (n=161) (97). The patients enrolled in this study received usual tocilizumab dose of 8 mg/kg every four weeks (97). The efficacy of tocilizumab after 6 months of treatment was assessed according to EULAR response criteria (98). Good EULAR response was lower in elderly than in younger patients (40.7% vs 61%; p=0.001) (97). On the other hand, there was no difference in moderate EULAR response between age groups. Also, remission was less frequently achieved in elderly patients compared to younger patients with rheumatoid arthritis (97). Regarding the safety of tocilizumab, no difference in
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ADVERSE EVENTS DISCONTINUATION RATES BETWEEN ELDERLY AND YOUNGER RHEUMATOID ARTHRITIS PATIENTS WAS DETECTED (97). HOWEVER, THE AUTHORS DO NOT RULE OUT THE POSSIBILITY THAT TOCILIZUMAB WAS PRESCRIBED MAINLY TO THOSE ELDERLY PATIENTS WITH BETTER GENERAL HEALTH CONDITION. ICHIBAN, A PROSPECTIVE STUDY THAT ASSESSED LONG-TERM EFFECTIVENESS AND SAFETY OF TOCILIZUMAB AMONG PATIENTS WITH RHEUMATOID ARTHRITIS IN DAILY GERMAN PRACTICE, SHOWED SIMILAR EFFICACY OF TOCILIZUMAB THERAPY IN ALL EXAMINED AGE GROUPS (<50, 50-65, AND >65 YEARS). FURTHERMORE, ADVERSE EFFECTS DISCONTINUATION RATES AND INCIDENCE OF INFECTIONS DID NOT SIGNIFICANTLY CHANGE WITH AGE (99,100).

SARILUMAB IS A HUMAN MONOCLONAL ANTIBODY DIRECTED AGAINST THE IL-6 RECEPTOR ALPHA, MEMBRANE-BOUND OR SOLUBLE FORMS, WITH GREATER RELATIVE BINDING AFFINITY FOR THE TARGET RECEPTOR THAN TOCILIZUMAB (101, 102). MOREOVER, IN COMPARISON WITH TOCILIZUMAB, IT INHIBITS IL-6 INDUCED CELLULAR RESPONSE AT LOWER CONCENTRATIONS (102). SARILUMAB IS ADMINISTERED AS A SUBCUTANEOUS INJECTION IN THE RECOMMENDED DOSE OF 200 MG ONCE EVERY TWO WEEKS (86,87). A POOLED EXPLORATORY ANALYSIS FROM MOBILITY AND TARGET TRIALS, EVALUATING EFFICACY AND SAFETY OF SARILUMAB IN RHEUMATOID ARTHRITIS PATIENTS AGED 65 YEARS AND ABOVE AND IN RHEUMATOID ARTHRITIS PATIENTS UNDER 65 YEARS, SHOWED COMPARABLE EFFICACY OF SARILUMAB (150 AND 200 MG) BETWEEN TWO AGE GROUPS ACCORDING TO ACR 20 RESPONSE RATES, DISEASE ACTIVITY SCORE IN 28 JOINTS USING C-REACTIVE PROTEIN (DAS28-CRP) REMISSION RATES, AT WEEK 24, IMPROVEMENT FROM BASELINE IN DAS28-CRP AND CLINICAL DISEASE ACTIVITY INDEX (CDAI) AT WEEK 24, AND ACCORDING TO CHANGE IN PHYSICAL FUNCTION FROM BASELINE ASSESSED BY THE HEALTH ASSESSMENT QUESTIONNAIRE-DISABILITY INDEX (HAQ-DI) AT WEEK 12 (103). SEVERE ADVERSE EVENTS, SUCH AS SEVERE INFECTIONS, DEVELOPED MORE FREQUENTLY IN RHEUMATOID ARTHRITIS PATIENTS AGED 65 YEARS AND ABOVE THAN IN YOUNGER PATIENTS (103).

EFFICACY AND SAFETY OF INTERLEUKIN INHIBITORS IN ELDERLY PATIENTS WITH PSORIASIS AND PSORIATIC ARTHRITIS

THE INTERLEUKIN INHIBITORS, FROM THE BIOLOGICS ARMAMENTARIUM FOR PSORIASIS AND PSORIATIC ARTHRITIS, TARGETED AGAINST CYTOKINES PIVOTAL FOR THE IMMUNOPATHOGENESIS OF PSORIASIS AND PSORIATIC ARTHRITIS, OR AGAINST THEIR RECEPTORS, ARE IL-12/23 AND IL-17 INHIBITORS (104,105). ALSO, BIOLOGICS AIMING P19 SUBUNIT OF IL-23 WERE SHOWN TO BE EFFICIENT IN THE TREATMENT OF PSORIASIS (104).

USTEKINUMAB IS A HUMAN MONOCLONAL ANTIBODY THAT TARGETS THE P40 SUBUNIT SHARED BY BOTH CYTOKINES IL-12 AND IL-23 (106). IT IS APPROVED FOR THE TREATMENT OF MODERATE-TO-SEVERE PLACED PSORIASIS, BUT ALSO FOR THE TREATMENT OF PSORIATIC ARTHRITIS IN ADULTS (107,108). IN ELDERLY PATIENTS WITH PSORIASIS (N=24), THE SAFETY AND EFFICACY OF USTEKINUMAB WAS ASSESSED OVER A PERIOD OF ONE YEAR (109). USTEKINUMAB WAS ADMINISTERED SUBCUTANEOUSLY AT RECOMMENDED DOSAGE. THE MOST FREQUENT COMORBIDITIES AMONG PATIENTS WERE CARDIOVASCULAR DISEASES (62.5%). ALSO, METABOLIC DISORDERS (37.5%), LATENT TUBERCULOSIS (29.2%) AND OTHER COMORBIDITIES WERE PRESENT IN THESE PATIENTS. THE EFFICACY WAS EVALUATED ON THE BASIS OF PSORIASIS AREA AND SEVERITY INDEX (PASI) AND THE DERMATOLOGY LIFE QUALITY INDEX (DLQI). GIVEN THE PROPORTION OF PATIENTS THAT HAD 75% OR MORE
reduction in PASI score (PASI 75) in the patient group that had received ustekinumab treatment before other biologics, and in the patient group that hadn’t been previously treated with biologics, a significantly greater improvement was reported in the latter group (109). Taking into account the total number of patients enrolled, PASI 75 was achieved in 60% at week 52 (109). However, ustekinumab treatment showed to be efficient in elderly psoriasis patients, and at the same time no severe adverse events were detected (109). Megna et al. (2016) performed a retrospective study of the efficacy and safety of ustekinumab in elderly patients (n=22) over a two-year period, and they obtained results similar to the ones previously described (110). Namely, PAS 75 was reached in 86.4% of patients at week 52 and in 90.9% of patients at week 100. Moreover, the two-year period of ustekinumab treatment was without severe adverse events (110). Therefore, even though these studies did not encompass such a large number of elderly psoriasis patients, the results suggested that ustekinumab may be considered a preferable agent for elderly psoriasis patients. As regards the use of ustekinumab in the treatment of elderly patients with psoriatic arthritis, relevant data were obtained from the PsABio study (111). The PsABio study was undertaken in order to collect data on patients with psoriatic arthritis receiving either ustekinumab or TNF inhibitors as first, second or third line of biologic DMARD treatment, and included 458 patients with psoriatic arthritis, of whom 22.9% were aged 60 years and older (111, 112). Gossec et al. (2020) reported PsABio results related to the comparison of the efficacy and safety of ustekinumab therapy, maintained from 6 to 12 months, between elderly and younger patients. Actually, the effectiveness and safety of ustekinumab therapy were comparable between two age groups (112).

The approved indications for secukinumab, human monoclonal anti-IL-17A antibody, are moderate to severe plaque psoriasis, active psoriatic arthritis, and active ankylosing spondylitis in adult patients (43,113). The results from two-year retrospective observational study by Megna et al. (2020) showed that treatment with secukinumab in patients with psoriasis age 65 or older was effective, judging by the significant reduction of PASI and body surface area (BSA) (114). The final mean PASI and BSA reduction was 85.1% and 88%, respectively (114). Secukinumab treatment was discontinued by 6 patients of a total number of 29 patients enrolled in this study, and in most cases the discontinuation was due to loss of response during the treatment. Furthermore, no severe adverse effects were reported during the two years covered by the study (114). A pooled post-hoc analysis of three phase III trials (ERASURE, FIXTURE and CLEAR) was performed in order to assess the efficacy and safety profile of this monoclonal anti-IL-17A antibody in elderly patients with moderate to severe plaque psoriasis (115). According to PASI and DLQI, this monoclonal anti-IL-17A antibody was found to be efficient in elderly patients. Moreover, the observed efficacy was comparable between elderly (n=67) and younger patients (N=841). More precisely, PAS 75 was achieved by 81.8% of elderly psoriasis patients and 79.4% of patients younger than 65 years by week 52 (115). Secukinumab administered at a recommended dose of 300 mg subcutaneously showed no difference in the total rate of adverse events in elderly and younger patients.
Nevertheless, the occurrence of severe adverse events, which were most likely related to secukinumab treatment, was higher in elderly patients (4.5% vs 1.8%), and these patients more frequently discontinued treatment compared to younger patients (7.5% vs 1.8%) (115). The results of long-term studies demonstrated a favorable efficacy and safety profile of secukinumab in the treatment of psoriatic arthritis (116,117), but, to the best of our knowledge, there are no studies that analyze the efficacy and safety profile of this interleukin inhibitor in elderly patients with psoriatic arthritis.

After secukinumab, another IL-17A inhibitor, ixekizumab, was approved for the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis (45,118). Ixekizumab is a humanized monoclonal antibody directed against IL-17A (119), which is believed to be the key effector cytokine in the patogenesis of psoriasis (120,121). A retrospective real-life study of the efficacy and safety of ixekizumab over a one-year period included 16 elderly (≥65 years) psoriasis patients (122). Psoriatic arthritis as a comorbidity was present in 9 patients. Moreover, most of these patients (n=14) had been previously treated with biologics (122). A remarkable improvement was found in these patients, judging by PASI 75 achieved by 93.7% at week 12, and by 100% improvement in PASI score (PASI 100) achieved by 81.2% at week 48 (122). Throughout the observed treatment period, no serious adverse events were reported, although one patient discontinued the therapy because of inadequate control of psoriatic arthritis (122).

Brodalumab is a human monoclonal antibody with high affinity to the IL-17 receptor A (123), approved for the treatment of moderate to severe plaque psoriasis in adults (44,124). In a pooled analysis, the data from phase III studies AMAGINE-1 and AMAGINE-2, undertaken to assess the safety and efficacy of brodalumab at two different doses (140 mg and 210 mg) (125,126) were stratified by two age groups (<65 and ≥65 years) (127). The patients received brodalumab every 2 weeks (140 mg or 210 mg), ustekinumab according to labeled dosing regimen, or placebo (127). The effectiveness of the treatment was assessed by PASI score and static physician’s global assessment (sPGA). The response rates of PASI 100 from baseline in elderly and younger psoriasis patients receiving brodalumab were 56.9% and 58.1%, respectively, at week 120. Similarly, taking into account the sPGA score, a comparable efficacy of brodalumab was found among elderly and younger psoriasis patients. Also, no difference in treatment-emergent adverse events rates between these two age groups was detected (127). A long-term evaluation of the efficacy and safety of modern treatments for psoriasis, that included 154 patients of Greek origin aged 65 years and older, showed a fast efficacy according to PASI 75 and 90% reduction in PASI score (PASI 90) response rates, but also sustained efficacy of brodalumab, secukinumab and ustekinumab (128). In fact, 16 patients had brodalumab treatment, and all of them achieved PASI 75 at week 12, and PASI 90 at week 24, and this efficacy of brodalumab was maintained for up to three years (128).

Guselkumab is a human monoclonal antibody, and tildrakizumab and risankizumab are humanized monoclonal antibodies, that selectively bind p19 subunit of IL-23, blocking its action on the IL-23 receptor (129). Guselkumab, tildrakizumab and
risankizumab were approved by FDA in 2017, 2018 and 2019, respectively, for the treatment of moderate to severe plaque psoriasis (46,47,48). Real-life studies of efficacy and safety of these IL-23p19 antagonists in elderly patients are lacking. The package insert of the drug reports that a total of 185/3406 subjects with plaque psoriasis or psoriatic arthritis exposed to the guselkumab in clinical trials were 65 years or older and 13 subjects were 75 years or older (46). As for tildrakizumab, the package insert of the drug reports that a total of 92/1083 subjects exposed to this IL-23p19 antagonist in clinical trials were 65 years and older, and 17 subjects were 75 years and older (47). When it comes to risankizumab, a total of 243/2234 subjects with plaque psoriasis exposed to this drug in clinical trials were 65 years and older, and 24 subjects were 75 years and older (48). The efficacy and safety profiles of all three IL-23p19 antagonists were comparable between elderly and younger subjects (46,47,48).

**Conclusion**

Although most of the reviewed findings may be limited by sample sizes, they suggest that interleukin inhibitors approved and currently in use in clinical practice for the treatment of rheumatoid arthritis, psoriasis, and psoriatic arthritis can be considered a safe and efficient option for these diseases in elderly patients. Bearing in mind that these diseases with elderly-onset have, to some extent, different characteristics than when they start earlier, such as clinical and laboratory manifestations, and possibly differences in genetic background and immunopathogenesis, studies are required to assess the efficacy and safety of interleukin inhibitors specifically in these patients.

**References**


Bezbednost i efikasnost inhibitora interleukina u terapiji reumatoidnog artritisa, psorijaze i psorijaznog artritisa u populaciji starih osoba

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Kratak sadržaj

Stariji pacijenti koji boluju od reumatoidnog artritisa, psorijaze ili psorijaznog artritisa uključuju one kod kojih je bolest imala kasni početak, nakon 60. godine starosti, ali takođe i one pacijente kod kojih je bolest počela ranije, a koji su ušli u stari doba. Imajući u vidu starenjem uslovljene promene imunskog sistema, moguću slabost starijih, podložnost infekcijama, prateći komorbiditet, koji uključuje i uzimanje više lekova, terapija ovih bolesti kod starijih pacijenata može predstavljati izazov. Inhibitori interleukina su se pokazali kao efikasna i bezbedna terapija ovih poremećaja. Međutim, stariji pacijenti sa ovim bolestima su često bili nedovoljno zastupljeni u ključnim kliničkim ispitivanjima inhibitora interleukina da bi se moglo sa sigurnošću utvrditi da postoji razlika u terapijskom odgovoru kod ovih pacijenata u odnosu na isti kod mladih pacijenata. Cilj ovog rada bio je da prikaže nalaze od značaja za bezbednost i efikasnost terapije inhibitorima interleukina kod starijih pacijenata sa reumatoidnim artritisom, psorijazom ili psorijaznim artritisom. Nalazi ukazuju da je efikasnost inhibitora interleukina, prikazanih u ovom radu, upoređiva kod starijih i mladih pacijenata. Osim toga, incidencija neželjenih događaja se nije razlikovala između ove dve starosne grupe. Veća incidencija teških neželjenih događaja kod starijih pacijenata u odnosu na mlade bila je zabeležena u terapiji reumatoidnog artritisa sarilumabom i psorijaze secukinumabom. Terapija reumatoidnog artritisa, psorijaze i psorijaznog artritisa inhibitorima interleukina može se smatrati efikasnom i bezbednom u populaciji starih pacijenata.

Ključne reči: inhibitori interleukina, stari pacijenti, bezbednost, efikasnost