ORIGINAL SCIENTIFIC ARTICLE

ADVERSE EFFECT IN PATIENTS WITH PSORIASIS TREATED WITH INTERLEUKIN 17A INHIBITOR- SECUKINUMAB

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ABSTRACT

Secukinumab is fully human monoclonal antibody, IgG-1κ, which selectively attaches to IL-17A and inhibits its effects, which subsequently leads to a decrease of local inflammatory markers. In 2015 it was approved for treatment of patients suffering from psoriasis. We can say that in comparison with other biologic medicine, such as IL-12/23 inhibitors and TNF-α inhibitors, the incidence rate of serious adverse effects related to use of secukinumab is notably lower. Serious adverse effects reported in relation to use of secukinumab were development of mucocutaneous candidiasis, neutropenia and development or aggravation of the inflammatory bowel disease conditions.
In this review study we focused on frequent adverse effects and adverse effects of special interest during the secukinumab therapy in treating psoriasis patients.
Available data on long-term safety and effects on comorbidities are relatively few. A more extensive and longer term research is needed, as well as critical reevaluation of the criteria for participation in clinical trials in order to obtain data which would be of relevance in clinical practice. A better understanding of adverse effects leads to an improved individual therapeutic approach, increases patient's satisfaction and results in minimizing these effects.

Keywords: *psoriasis, biological agents, adverse events, secukinumab, IL-17.*

INTRODUCTION

Psoriasis is a multisystem inflammatory, immune-mediated disease which affects 1 – 3% of the world population (1). The immunopathogenesis and the genetic basis of psoriasis have not yet been fully understood. While the epidermal hyperproliferation was considered to be the major pathogenetic mechanism behind psoriasis, contemporary findings point out to the crucial role of the immune system, primarily the role of T lymphocytes. An improved understanding of the mechanisms behind the psoriasis will result in better therapeutic approach (2, 3, 4, 5). Immunomodulators have proven to be highly efficient in treating psoriasis. Antagonists which commonly in use today are: tumor necrosis factor (TNF), IL-12/23, IL-17 (2). The interleukin 17 family comprises: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. High concentrations of IL-17 (IL-17A, IL-17C, IL-17F) family have been detected in the psoriatic lesions of diseased patients in comparison to healthy individuals, while IL-17 has positive correlation with the severity of disease (5). IL-17F and IL-17A are covalent homodimers and send signals through the same receptor subunits (IL-17RA and IL17RC), although IL-17A is 20-30 times more potent in activating gene expression (6). IL-17 is one of the key cytokines in the psoriasis pathogenesis because apart from activating the proliferation of keratinocytes, it also induces creation of antimicrobial peptides, cytokines, and chemokines, which subsequently activate other cells thus leading to amplification of inflammation (7). The IL-17A inhibitors used for treating the psoriasis today are secukinumab and ixekizumab, while brodalumab is the drug which inhibits IL-17RA (8).

Secukinumab (Cosentyx®, Novartis) is fully human monoclonal antibody, IgG-1κ, which selectively attaches to IL-17A and inhibits its attachment to receptors, which subsequently leads to a decrease of local inflammatory markers (9). Fully human antibodies imply lower risk of suppression of the patient's immune system, i.e. they are less immunogenetic (10). Efficiency and safety of Secukinumab have been proven in phases II (11) and III (12, 13) of clinical research, which led to its approval for use in psoriasis treatment by the European Medicines Agency (EMA) and American Food and Drug Administration (FDA) in 2015 (14). Considering that psoriasis is a chronical disease, it may sometimes require a lifelong treatment. Monitoring of the psoriasis therapy efficiency and the safety profile of these drugs *facilitates better monitoring of the patient's overall condition and potential comorbidities and can give us screening guidelines which would result in an increase of the* Healthy life expectancy (HALE). More comprehensive and long-term studies are needed to obtain precise information on unexpected and infrequently reported adverse effects (AE) which might have correlation with a prolonged use of secukinumab.

We searched on PubMed and Web of Science up to August 2021 all studies on secukinumab adverse events in Psoriasis. The following search terms were used: "secukinumab", "anti-IL-17", "adverse events", "interleukin 17A blockers" and "safety of biologic". We focused on clinical trial and meta-analysis, although other relevant studies were considered. The aim of this paper is to provide an overview of safety profile secukinumab in psoriasis patients. In addition, we discuss the impact of other biologics agents vs secukinumab.

COMMON ADVERSE EVENTS AEs

Secukinumab is a biological medicine which has so far proven its efficiency and a favorable safety profile (15, 16). It is a new generation drug and for this reason we still have a limited knowledge of its safety profile. Some clinical studies report infections in patients who were treated by secukinumab (Table 1). Most of them were mild to moderate infections of the upper respiratory tract, such as nasopharyngitis, and did not require the interruption of the treatment. The JUNCTURE study (17) also reported the nasopharyngitis as the most common adverse effect, mostly mild to moderate (31% on 300mg; 23.0% on 150mg), in comparison to placebo (16.4%). In a research dealing with the safety of secukinumab in treatments of older patients some AE were reported to be more frequent in older patients, namely, nasopharyngitis was reported in 26.1% of older patients examined, in comparison to 19.4% of younger patients. Furthermore, headache was reported to be more frequent in older examinees (13.7% versus 6.0%), as well as oropharyngeal pain (0.0% versus 7.0%) and influenza (6.7% versus 3.0%). The study also suggests that some common AE are more frequent in younger individuals, such as pruritus (10.4% versus 5.1%), hypertension (10.4% versus 4.3%), eczema (7.5% versus 3.6%), and diarrhea (9.0% versus 7.7%) (18).

ADVERSE EVENTS OF SPECIAL INTEREST

One of the most common AEs of special interest for secukinumab is mucocutaneous candidias, which rarely leads to medication discontinuation (23). Other AEs of special interest are neutropenia, inflammatory bowel disease and major adverse cardiovascular events, and their monitoring is required although their incidence rate is not high (24, 25, 26).

CANDIDA INFECTIONS

Interleukin 17A plays an important role in an innate and adaptive response to skin and mucosa infection, such as chronic mucocutaneous candidiasis (CMC) infection of mucosa, nails, and skin in patients with lower IL-17 response (27, 28). IL-17 mediated immunity is crucial for protection of mucosa and skin from *Candida albicans*, so that a higher incidence rate of candida infection can be expected in patients treated by interleukin 17 inhibitors (29). A study covering 9 phases of the level II of clinical research and 10 phases of the level III of clinical research reports a higher incidence rate of candida infection in secukinumab treatment (3.1%) in comparison to entanercept (1.4/%), ustekinumab

(1.6%) and placebo (1.7%). It was also indicated that the incidence rate significantly decreases after one year, with 2.0% in the second year and lowering to 0.3% in the fifth year (26). A higher incidence rate in the group treated by secukinumab (4.7% on 300 mg; 2.3% on 150 mg) in comparison to etanercept (1.2%) is also reported by the FIXTURE study (30). In comparison to other biological medicine used for the treatment of psoriasis, incidence rate in secukinumab was 3.3%, brodalumab 4.0%, ustekinumab 2.3%, etanerecept 0.8% while the incidence in case of placebo was 0.3% (23).

IBD (IMFLAMATORY BOWEL DISEASE)

In comparison with the general population where the estimated prevalence of Inflammatory Bowel Disease (IBD) was 0.4%, in patients diagnosed with psoriasis the prevalence was 1-2% (31). IBD can be manifested in two ways: ulcerative colitis (UC) and Crohn's disease (CD) (32). Studies have shown that the use of the secukinumab in psoriasis treatment does not lead to statistically significant incidence of development or aggravation of IBD. The incidence rate throughout the 52 weeks study for secukinumab (0.33%) and etenercept (0.34%) was similar. The incidence rate adapted to exposure to Crohn's disease was 0.11% and for ulcerative colitis 0.15%. There was no clinically significant difference between incidence rates in the first 12 weeks and the remaining 52 weeks (33, 30). Although IBD also appears in patients who did not have gastrointestinal symptoms before and do not have family history of the same, a detailed research into both family history of the disease and the symptom history is required before introducing the IL-17 inhibitors. Although rare, cases of development of IBD are reported in the literature (34, 35, 36, 21). It is known that IL-17 can have protective role in IBD, so inhibition of IL-17 can result in imbalance, which explains the appearance of symptoms related to IBD (37).

NEUTROPENIA

It is common knowledge that interleukin 17A produces cells called neutrophil-regulatory or Tn cells (38), therefore, secukinumab can cause hematological disorders, such as a decrease in the number of neutrophils. In a 52 weeks study, 1st degree neutropenia appeared or was aggravated in 77% of subjects, while the 2nd degree neutropenia developed more frequently in subjects using etanercept. 3rd degree neutropenia developed in 0.5% subjects during the treatment with secukinumab and 0.1% in the group receiving placebo. 4th degree neutropenia was reported in 0.3% subjects using etanercept and no cases were reported related to the treatment with secukinumab (33). Although it is obvious from the literature that neutropenia is rare and most often mild, periodical observation is recommended.

MACE (Major adverse cardiovascular events)

In their meta-analysis, Armstrong et al. report that the patients with difficult cases of psoriasis have an increased risk of Major Adverse Cardiovascular Disease (MACE). The risk of the cardiovascular death in these patients was increased by 39%, the risk of stroke was increased by 56% and the risk of the myocardial infarction by 70% in comparison to general population (39). The meta-analysis which covered 38 randomized clinical studies showed that there was no statistically significant risk of MACEs in patients diagnosed with psoriasis receiving biological treatments (adalimumab, etanercept, infliximab, ustekinumab, secukinumab and ixekizumab) in comparison to the placebo groups. Furthermore, there is no difference between licensed doses of neither ustekinumab (45mg versus 90mg), nor secukinumab (150mg versus 300mg) (40). In a study carried out in 2014 and covering 177 examined cases, two serious adverse cardiovascular incidences were reported (41), while just one year earlier, a study covering 4 times more subjects reported zero MACEs in 737 examinees.

ISR (Injection-site reactions)

In a study which analyzed the differences in incidence rates of the injection site reaction (ISR) in biological drugs approved for the treatment of psoriasis, out of the total number of registered cases, the lowest number was associated with ustekinumab (8), then etanercept (144), followed by secukinumab (654) and ixekizumab (1771), while the highest number of ISRs was related to adalimumab (15.637). The most common injection site related event from the total percentage of ISRs associated with secukinumab was bruising, which appeared in 25.7% cases, pain in 25.4%, followed by hemorrhage 12.5%, swelling 7% and erythema was registered in 4.9% examinees (42). Contrary to these findings, the FIXTURE study reports a lower incidence (0.7%) of ISRs in the group treated by secukinumab than in the one treated by etanercept (11%) (12). Paul et al. in their study (17) also report low percentage (1.36%) of ISRs, which were all mild or moderate.

COMPARISON OF SAFETY WITH OTHER BIOLOGIC DRUGS

In the GESTURE study, the total incidence rate of adverse effects was somewhat higher in case of the treatment with secukinumab 150mg (88.9%) in comparison to 300mg (80%). Similar data is provided by Papp et al. (44), where the incidence rate of AE was higher in the 150mg (89%) group, than in other doses of secukinumab (73-16%), which was similar to the placebo group (73%). Data on the incidence rate related to exposure in 10 phases I and phases II for psychic disorders demonstrate that the incidence rate for the 300mg secukinumab was 4.17%, for the 150mg secukinumab therapy was 6.15%, and in the group treated by etenarcept 5.64% (33).

Data obtained by a meta-analysis which covered 28 studies and 19840 patients (45) show that the 150mg dose of secukinumab is more frequently associated with adverse conditions than ustekinumab 90mg, tildrakizumab 200mg and tildrakizumab 100mg. This analysis also covers some relatively new medicine - tildrakizumab licensed by FDA in

March 2018, and risankizumab in April 2019. More recent biological agents such as ustekinumab and secukinumab which inhibit IL-23/IL-17 have proven to be more efficient in comparison to TNF-α inhibitors. In clinical studies the adverse effects profile of IL-17a is mostly limited to mild inflammations of the respiratory tract, inflammation of the nasal part of the pharynx, back pain, and headache (46, 16, 44).

Incidence of serious adverse effects was reported, but they were in general lower in patients treated by inhibitors IL12/23 and IL-17 (47), while patients using anti-TNF were reported to have a higher risk of serious infections, such as reactivation of the hepatitis B, lymphoma and latent tuberculosis (48).

Table 1. Summary of phase 3 and phase 2 trials - the overall incidences of common reported adverse events Aes

Study	Phase	Duration (week)	Population	Years of publish	The most commonly reported AEs
Reich et. all (ECLIPSE) (19)	Phase 3	48	1048	2019	Nasopharyngitis (24%); Upper respiratory tract infection (18%); Headache (9%); Arthralgia (5%); Back pain (4%); Diarrhoea (4%)
Langley et. all (FIXTURE) (12)	Phase 3	52	738	2014	Nasopharyngitis (24.6%) Headache (11.2%) Diarrhea (7.9%)
Mrowietz et. all (2PRECISE) (20)	Phase 3b	52	237	2019	Nasopharyngitis (47.1%); Pustular psoriasis (28.5%); Headache (15.05%); Pruritus (14.11%); Pain in extremity (8.04%); Diarrhea (6.92%).
Warren et. all (IM-Merge) (21)	Phase 3	52	327	2021	Nasopharyngitis (16.56%); Headache (9.2%); Upper respiratory tract infection (8.59%); Arthralgia (6.13%); Diarrhoea (5.52%); Bronchitis (6.7%)
Wu et. all (ERASURE) (22)	Phase 3	52	51	2017	Upper respiratory tract infection (31.3%); Pruritus (37.5%); Hyperlipidemia (18.8%); Cough (12.5%); Folliculitis/furuncle (12.5%); Periodontitis (12.5%).
Ohtsuki et. all (EASURE) (13)	Phase 3	52	87	2014	Nasopharyngitis (26.8%); Eczema (8.7%); Furuncle (5.8%); Tineapedis (5.6%); Urticaria (5.6%)
Rich et. all (11)	Phase 2	12	404	2013	Nasopharyngitis (16.1%); Neutropenia (6.3%); Headache (5.9%); Upper respiratory tract infection (4.2%)

CONCLUSION

Development of biologic drugs marked a huge progress in the treatment of psoriasis. Based on our knowledge so far, the ration between benefits and risk of adverse effects justifies their use. By comparing the TNF-α inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors, we can see that the incidence rate of AEs is notably lower in IL-12/23 and IL-17 inhibitors. The interleukin 17 inhibitors have recently become available, and more information about them will be obtained in the coming period. Furthermore, interleukin 17, its function and its mechanism of action have not yet been fully explained, and future research in this field will help us understand adverse effects of this interleukin's inhibition (49). The available data shows that the majority of users of biologic medicine are different from those covered by clinical trials, because patients who are not eligible for phase III are more susceptible to developing adverse events, and they are excluded from the research. The safety profile of biologic drugs in the real world in case of users who are not suitable to be included in research, is less favorable than the safety profile achieved in clinical research (50). Critical reevaluation of the criteria for inclusion in the phase III is necessary in order to obtain more relevant data.

Different biologic drugs are currently available for the treatment of psoriasis, and secukinumab is one of them. Compared to other drugs, secukinumab had a better safety profile in numerous studies in relation to more serious adverse effects (51, 52, 47). On the other hand, it is more frequently related to Candida, neutropenia and IBDs, which explains the common role of IL-17 in these disorders and the psoriasis itself.

Available data on the long-term safety and effects on comorbidities are relatively scarce. More research in this field is necessary. A better understanding of adverse effects leads to an improved individual therapeutic approach, increases the patient's satisfaction and results in minimizing these effects.

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