



Review of Ph.D. Thesis.

Oponentský posudek dizertační práce „ Nežádoucí účinky biologické léčby psoriázy (Adverse events of biologic therapy in psoriasis)

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The doctoral thesis is formed of 222 pages in English, divided into 4 Chapters. Otherwise the whole work as arranged in the table of content include 15 topics where each topic includes several subtopics (3-8 subtopics). After the introduction (8 pages), the goal of the thesis is well written (7 pages)). Each chapter has its own sections including materials and methods, results, discussion, conclusions and the relevant references.

This doctoral thesis focuses on psoriasis vulgaris and its therapy, especially biologic agents and their safety profiles. The objectives of this research were to identify prognostic factors of severe psoriasis, compare the safety profiles of different therapy types (topical compounds, non-biologic

systemic agents) and those of biologic agents (adalimumab, etanercept, infliximab, secukinumab, ustekinumab). A total of 289 psoriatic patients were followed up for 30 months; at disease onset, viral upper respiratory infections and periods of hormonal changes seem to be prognostic of higher levels of psoriasis severity. When comparing therapy types, biologic agents were the most effective therapies; however, they were associated with higher rates of adverse events and treatment discontinuation. A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile.

I appreciate that the author reported at the beginning of page 6, a list of abbreviations used throughout the whole work. The last chapter of this thesis includes the author publications (in extenso), that are related to the doctoral thesis (3 with impact factors and 3 without IF, unrelated to the doctoral theses (with or without IF 10) in addition to several others in the form of posters or oral presentations .

An overall results and discussion is presented with references are included followed with the main part of references and an overall discussion and conclusion (pp 161-197). Summary of the doctoral thesis (autoreferát, téze) is in English language, has 29 pages in accordance to the act of the Ph. study in biomedicine §16, odst.3. The topic of this thesis is realistic since it is directed to the unwanted effects of the of biologic therapy in psoriasis with the goals:

1. To establish possible trigger and prognostic factors of severe psoriasis.
2. To compare the occurrence of adverse events in three groups of psoriatic patients on different therapeutic regimens, aiming to determine the type of therapy with the lowest safety profile.
3. To investigate and compare possible differences in the occurrence of adverse events in individual groups of patients with psoriasis treated with different biologic agents.

The goal of the thesis was fulfilled with rigorous experimental and clinical approaches,

The results are reported in various chapters are in full text available in the attached copies of the authors work.

The thesis involves original results which were published by the author as full original articles that were reviewed by the experienced reviewers of the relevant scientific journal under the strict regulations of various scientific journal.

It was concluded that psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia, and nonspecific noninfectious liver disease. Male gender, increased height, early age at disease onset, viral upper respiratory infections and periods of hormonal changes seem to be prognostic of higher levels of psoriasis severity. When comparing therapy types, biologic agents were the most effective therapies; however, they were associated with higher rates of adverse events and treatment discontinuation. A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. The results are well documented in the form of Tables and Figures. Detailed results of each study are provided in the doctoral thesis.

During the follow up, BAs were associated with the lowest safety profile when compared with the other forms of treatment. Patients treated with BAs showed higher overall rates of AEs.

- This research reveals the use of increased height and puberty, menopause/andropause as independent prognostic factors of psoriasis severity.

Why the height is an important prognostic factor in determining the psoriasis severity?

The authors results reveal that adverse effects produced by topical agents are the lowest. This raises the question:

Why we should use biological agents systemically ?

The Food and Drug Administration (FDA) has approved a new drug for the treatment of moderate to severe plaque psoriasis. The drug, called deucravacitinib, that is the first TYK2 inhibitor approved for the treatment of many diseases.

Would you comment on these findings and what is the present status of this medicine(s) in psoriasis management?

The author came to the conclusion that a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic agent treatment.

- In spite of the reasonable quality of the work in general with all aspects of research work I have the following comment,

the detachments of various aspects on psoriasis adverse events of biologic therapy as reported in the thesis seem a little confusing and it might be better to put all results of various studies under one or two topics. In fact you are writing a thesis rather than writing a book (i.e. bookish type).

However, my comments have nothing to do with the quality of research reported in this thesis.

Disertace obsahuje originální výsledky, které autor disertace publikoval jako původní práce v plném znění ve vědeckých časopisech s IF a které tedy prošly recenzním řízením. Závěrem mohu konstatovat, že předložená dizertace splňuje

požadavky §16 řádu doktorského studia biomedicíny, tj. je uceleným vědeckým pojednáním se zajímavými a metodicky kvalitně získanými vlastními původními výsledky. Disertační práce prokazuje předpoklady MUDr. Emanuel Carvalho MARQUES k samostatné tvořivé vědecké práci a k udělení titulu „Ph.D.“ za jménem.

Professor Hassan Farghali, Ph.D., D.Sc.

Praze, 6. března 2023

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