Research Protocol:

Association of hydrocortisone use for atopic dermatitis on coronavirus disease (COVID19) incidence and severity (Characterization)

About this research protocol:

This research will be written by Akari Kira, as a part of my Extend Essay for International Baccalaureate Organization (IBO) to evaluate my research design skill and essay writing skill. IBO requires students' individual work, and prohibits any comments and feedback. However, it is impossible to conduct multinational big data analysis without using OHDSI tools, and data networks.

After the final submission, (possibly around Dec. 2021), submitted research will be pasted in the Appendix. And review cohorts, analysis methods on ATLAS, rewrite the protocol if needed.

Acknowledgement:

The analysis is based in part on work from the Observational Health Sciences and Informatics collaborative. OHDSI (http://ohdsi.org) is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics.

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1. List of abbreviations

AD	Atopic Dermatitis
AGEP	acute generalized exanthematous pustulosis
ATC	Anatomical Therapeutic Chemical Classification System
CDM	Common Data Model
COVID-19	Coronavirus Disease 2019
IL-1	Interleukin 1
IL-6	Interleukin 6
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
RxNorm	US-specific terminology in medicine that contains all medications available on the US market
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SNOMED	Systematized Nomenclature of Medicine
TNF-α	Tumour Necrosis Factor alpha

2. Responsible Parties

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3. Abstract

This study protocol focuses on characterization analysis through ATLAS provided by OHDSI. Data will then be evaluated for the association between prevalent use of hydrocortisone among atopic dermatitis patients and the risk of contracting COVID-19 infection and severity such as mechanical ventilation. The evaluation will also be done by comparing the data obtained with data from Charybdis (Characterizing Health Associated Risks, and Your Baseline Disease In SARS-COV-2). If the data shows positive correlation or association, comparative study will be planned as a OHDSI network study.

4. Amendments and Updates

Date	Section Number	Amendments or Updates	Reason

5. Milestones

Milestones	**Scheduled Date**
Complete Study Protocol	January 11th 2021
Start Analysis	February 20th 2021
End Analysis	March 5th 2021
Review Protocol	November 2021
Start Analysis	
End Analysis	

6. Rationale and Background

Since January 2020, the number of cases for COVID-19, caused by coronavirus SARS-CoV2 is increasing its number. Total number of confirmed cases overcomed 80 million and is responsible for more than 1.8 million deaths as of January 6th, 2021(*WHO Coronavirus Disease (COVID-19) Dashboard*, n.d.).

High severity and mortality of COVID-19 appears to be driven by cytokine storms, adverse production of cytokines such as IL-6, IL-1 and TNF-α (Soy et al., n.d.). Cytokine storms cause aggressive ARDS and result in multi-organ failure as the damage of tissues proceeds (Ragab et al., 2020) (Hojyo et al., 2020). These findings suggest the potential on using anti-inflammatory drugs, and WHO has published the protocols to treat severe COVID-19 patients on corticosteroids (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1).

Meanwhile, different types of skin rash can be observed as a symptom of COVID-19 (*Coronavirus Disease (COVID-19)*, n.d.; The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020). These are said to be acute generalized exanthematous pustulosis (AGEP), as a result of T cell-mediated neutrophilic inflammatory response (Haraszti et al., 2020). Rashes can be treated by using antihistamines and corticosteroids (Abuelgasim et al., 2020) (*Acute Urticaria Treatment & Management*, 2019).

So far, 7 clinical trials on phase 3 have completed (same source) which shows decrease in mortality and/or severity(The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020). Hydrocortisone, dexamethasone, prednisone, and methylprednisolone injections are suggested in the protocols (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1).

Atopic Dermatitis (AD) is the most common eczema, affecting more than 1% of the overall population(Avena-Woods et al., n.d.). AD is a type of allergic reaction by overreacting the immune system, detailed pathophysiology of AD is not concrete (W et al., 2017). The use of corticosteroids is an effective way to treat AD patients, by modulating proinflammatory cytokine signaling(*Atopic Dermatitis Treatment & Management*, 2020)(*Atopic Dermatitis Treatment & Management*, 2020; Blauvelt et al., 2017). Hydrocortisone and Dexamethasone, corticosteroids mentioned in the WHO protocol for Corticosteroids on COVID-19 are used to treat AD patients world wide https://www.dermatol.or.jp/uploads/uploads/files/guideline/atopic_GL2018.pdf? (*Appendix D. Topical Corticosteroids for the Treatment of Atopic Eczema, Grouped by Potency | Frequency of Application of Topical Corticosteroids for Atopic Eczema | Guidance | NICE*, n.d.; Eichenfield et al., 2014; Kim et al., 2015). Hence, exposure of cortisone steroids may affect their immune response, particularly

regulating cytosine production thus the risk of the long-term users of corticosteroids on COVID-19 would differ.

To this date, the study is focused on the results by the injectable corticosteroids as a treatment and its outcome. This study will be focusing on the long term exposure of corticosteroids used by atopic dermatitis patients and their outcomes regarding on COVID-19.

The OHDSI community offers the potential to conduct this analysis in observational data in the framework of scientifically stringent observational investigations. OHDSI provides access to international data assets mapped on Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). This allows us to conduct the research across a number of populations. ATLAS provides an interface to create a package of cohort definition and analysis pathways.

7. Study Objectives

Objective: To evaluate the association between prevalent use of hydrocortisone among atopic dermatitis patients and the risk of contracting COVID-19 infection and severity such as mechanical ventilation.

8. Research methods

Study Design

A series of multinational, multi-database network comparative cohort studies will be conducted, to include:

1. Characterization Study of Atopic Dermatitis Patients including demographic information, drug era, subgroup of hydrocortisone use and outcome of COVID-19 will be evaluated

Data Source(s)

Study population #1

The cohort will consist of adult patients aged 18 years who receive at least one eligible occurrence of *Atopic Dermatitis* before 31st January 2020 (with index date set as the last prescription in this window) and with at least 180 days of drug era. are observable in each database for at least 180 days

prior to the index date. Cohort exit will be the earliest of: the occurrence of an outcome event; the end of exposure; death; loss or deregistration from the database; or date of last data collection.

Subgroup Cohorts

The primary outcomes of interest will be an incident of COVID-19 diagnosis or SARS-CoV-2 positive test 1) without hospitalization, 2) with hospitalization, 3) requiring intensive in-patient services such as mechanical ventilation. The detailed definitions of these outcomes are given in Appendix 1. https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/documents/Protocol_COVID-19%20Charybdis%20Characterisation_V5.docx

Stratification

Feature of Interests

Feature of interest will be an exposure to corticosteroids (hydrocortisone or dexamethasone) after index date with 60 days of drug era. And less than 30 days of an exposure to corticosteroids after index date.

9. Data Analysis Plan

1. Characterization

Study Population 1 = Atopic Dermatitis (Cohort)

Outcome; Demographic Information, Ingredients (Corticosteroids), Age, Race, **COVID-19** diagnosis/hospitalization/severe

10. Strengths and Limitations of the Research Methods

Strength

Using OMOP CDM allows to conduct the research across a multiple database, thus with a larger population. This also allows us to investigate differences under diverse medical systems, ethics, and geography. Propensity score matching, and stratification strategies on balancing on a large number of baseline potential confounders will be used in addition to negative control outcomes to reduce residual bias in the study.

Limitation

Health care data for COVID-19 will increase in its amount but this method can not evaluate the association or show the most-recent data.

Drug concepts are all in RxNorm. Although OMOP CDM allows us to include all other concepts in RxNorm Extension, it is not a real time follow up. This can lead to misclassification of outcomes, through coding errors. Diagnostic and coding errors can also result in misclassification of outcomes. Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.

11. Protection of Human Subjects

The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

12. Management and Reporting of Adverse Events and Adverse Reactions

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events reports. The study results will be assessed for medically important results.

13. Plans for Disseminating and Communicating Study Results

The initial report will be submitted to IBO. Submitted reports will be assessed on designing the research, and writing of the research.

In order to do so, I need to design and write the research paper on my own. Research protocol, analysis pathways, and GitHub codes will be open to the public through OHDSI community.

After the final submission (possibly around Dec. 2021) to IBO, the research protocols including concepts, cohorts, and analysis plan will be re-evaluated in OHDSI community for further development. Final report will be published to OHDSI and will be reviewed.

14. Appendix

Appendix 1: Target, Comparator, and Outcome Cohort Definitions

Exposure cohort definitions [AS OF 6th JANUARY 2020]

Cohort Entry Events

People with continuous observation of 180 days after event may enter the cohort when observing any of the following:

condition occurrences of 'Atopic Dermatitis', starting on or before January 31, 2020 and ending on or after January 31, 2020.

Inclusion Criteria

1. Age >= 18

Entry events with the following event criteria: who are >= 18 years old.

Limit qualifying entry events to the earliest event per person.

Cohort Exit

The cohort end date will be based on a continuous exposure to 'Dermatological Corticosteroids': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

Subgroup cohort definitions

This section documents the outcome cohort definitions. We consider

- COVID-19 diagnosis or SARS-CoV-2 positive test with no required prior observation
- Hospitalization with a COVID-19 diagnosis record or SARS-CoV-2 positive test with no required prior observation
- Hospitalization and requiring intensive services with a SARS-CoV-2 positive test with no required prior observation

[COVID ID133 V1] Persons with a COVID-19 diagnosis or a SARS-CoV-2 positive test with no required prior observation
[COVID ID135 V1] Persons hospitalized with a COVID-19 diagnosis record or a SARS-CoV-2 positive test with no required prior observation
[COVID ID137 V1] Persons hospitalized and requiring intensive services with a CO

Appendix 2: ENCePP Checklist for Study Protocols

15. References

Abuelgasim, E., Dona, A. C. M., Sondh, R. S., & Harky, A. (2020). Management of urticaria in COVID-19 patients: A systematic review. *Dermatologic Therapy*, e14328–e14328.

Acute Urticaria Treatment & Management. (2019, November 10). https://emedicine.medscape.com/article/137362-treatment#d7

Appendix D. Topical corticosteroids for the treatment of atopic eczema, grouped by potency | Frequency of application of topical corticosteroids for atopic eczema | Guidance | NICE. (n.d.). Retrieved January 7, 2021, from https://www.nice.org.uk/guidance/ta81/chapter/Appendix-D-Topical-corticosteroids-for-the-treatment-of-atopic-eczema-grouped-by-potency

Atopic Dermatitis Treatment & Management. (2020, August 26). https://emedicine.medscape.com/article/1049085-treatment#d6

Avena-Woods, C., Pharm, B. S., Phar, & BCGP. (n.d.). *Overview of Atopic Dermatitis*. Retrieved January 6, 2021, from https://www.ajmc.com/view/overview-of-atopic-dermatitis-article

Blauvelt, A., de Bruin-Weller, M., Gooderham, M., Cather, J. C., Weisman, J., Pariser, D., Simpson, E. L., Papp, K. A., Hong, H. C., Rubel, D., Foley, P., Prens, E., Griffiths, C. E. M., Etoh, T., Pinto, P. H., Pujol, R. M., Szepietowski, J. C., Ettler, K., Kemény, L., … Shumel, B. (2017). Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*, *389*(10086). https://doi.org/10.1016/S0140-6736(17)31191-1

Coronavirus disease (COVID-19). (n.d.). Retrieved January 6, 2021, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19#:~:text=symptoms

Eichenfield, L. F., Tom, W. L., Berger, T. G., Krol, A., Paller, A. S., Schwarzenberger, K., Bergman, J. N., Chamlin, S. L., Cohen, D. E., Cooper, K. D., Cordoro, K. M., Davis, D. M., Feldman, S. R., Hanifin, J. M., Margolis, D. J., Silverman, R. A., Simpson, E. L., Williams, H. C., Elmets, C. A., … Sidbury, R. (2014). GUIDELINES OF CARE FOR THE MANAGEMENT OF ATOPIC DERMATITIS: Part 2: Management and Treatment of Atopic Dermatitis with Topical Therapies. *Journal of the American Academy of*

Dermatology, *71*(1), 116.

Haraszti, S., Sendil, S., & Jensen, N. (2020). Delayed Presentation of Acute Generalized Exanthematous Pustulosis Following Treatment with Cefepime in a Patient with COVID-19 without the Use of Hydroxychloroquine. *The American Journal of Case Reports*, *21*. https://doi.org/10.12659/AJCR.926901

Hojyo, S., Uchida, M., Tanaka, K., Hasebe, R., Tanaka, Y., Murakami, M., & Hirano, T. (2020). How COVID-19 induces cytokine storm with high mortality. *Inflammation and Regeneration*, *40*(1), 1–7.

Kim, J. E., Kim, H. J., Lew, B.-L., Lee, K. H., Hong, S. P., Jang, Y. H., Park, K. Y., Seo, S. J., Bae, J. M., Choi, E. H., Suhr, K. B., Lee, S. C., Ko, H. C., Park, Y. L., Son, S. W., Seo, Y. J., Lee, Y. W., Cho, S. H., Park, C. W., & Roh, J. Y. (2015). Consensus Guidelines for the Treatment of Atopic Dermatitis in Korea (Part I): General Management and Topical Treatment. *Annals of Dermatology*, *27*(5), 563.

Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R., & Salem, R. (2020). The COVID-19 Cytokine Storm; What We Know So Far. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.01446

Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (n.d.). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology*, 1.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne, J. A. C., Murthy, S., Diaz, J. V., Slutsky, A. S., Villar, J., Angus, D. C., Annane, D., Azevedo, L. C. P., Berwanger, O., Cavalcanti, A. B., Dequin, P.-F., Du, B., Emberson, J., Fisher, D., Giraudeau, B., Gordon, A. C., Granholm, A., Green, C., … Marshall, J. C. (2020). Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA: The Journal of the American Medical Association*, *324*(13), 1330–1341.

W, D. B., Tarbox, J. A., & Tarbox, M. B. (2017). Atopic Dermatitis: Pathophysiology. *Advances in Experimental Medicine and Biology*, *1027*.

https://doi.org/10.1007/978-3-319-64804-0_3

WHO Coronavirus Disease (COVID-19) Dashboard. (n.d.). Retrieved January 6, 2021, from https://covid19.who.int