Severe infection risks of biologics in psoriasis: some methodological critics

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Pros

- Large and high-quality registry data from European countries.
- Rigorous design and analysis (target trial emulation with new users of biologics, proportional hazard models, random effect Poisson regression, etc.).
- Important findings with large impact on clinical practice.

Selection of patients

- Yiu et al (2018) compare biologic-naive patients starting either a biologic or a non-biologic treatment.
  - Patients in the control group are prevalent users of non-biologics, which may increase the risk of confounding by indicator.
  - E.g. non-biologic patients at baseline who need not a biologic may be healthier than those who need to switch to a biologic.

Exposure and control definition

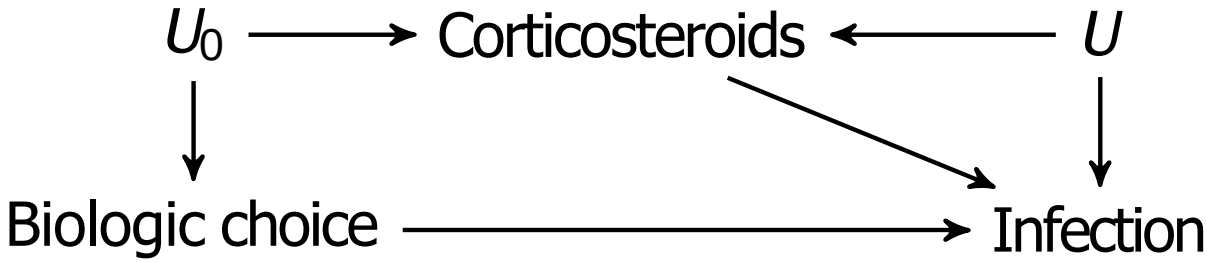
- Lluch-Galcera et al (2024) define the time of exposure to a systemic drug = last drug administration date/censoring date - start date of treatment
  - The exposure time is likely not well defined for censored patients.

Time-varying confounders

- Yiu et al (2018) and Penso et al (2021): Post-baseline concomittant immunosuppresants were adjusted as time-varying confounders in the Cox model.
- Lluch-Galcera et al (2024) consider baseline-confounders only. That is, data on the exposure and outcome are collected at multiple timepoints after baseline, but only confounders at baseline are adjusted for.

Post-baseline concomittant drugs

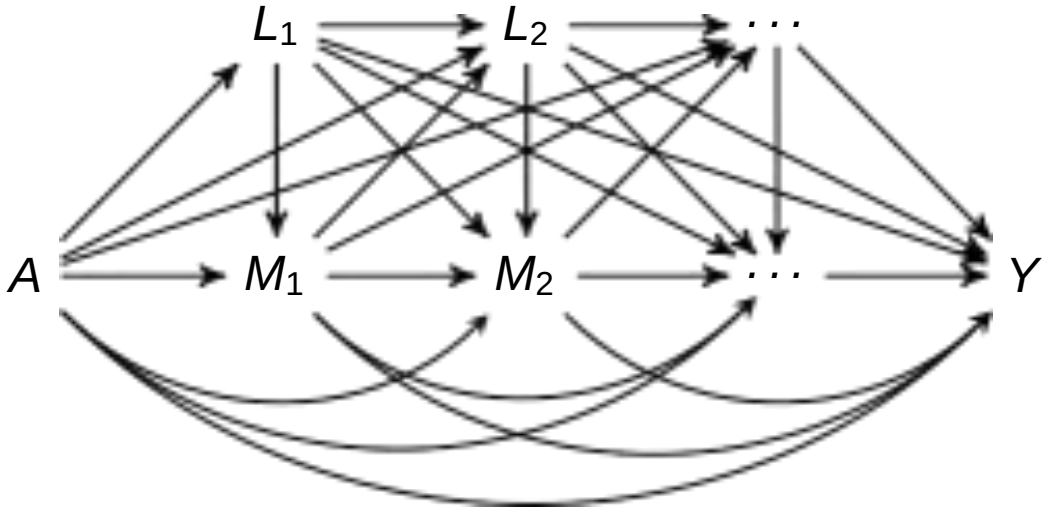
- Assume that we have data on biologic choices (at baseline), corticosteroid prescription (at month 3) and infection status (at month 6).
- Corticoid is very often prescribed after biologic initiation, which can increase infection risk.



- It is reasonable to want to adjust for corticoid use after baseline.
- But cautions are needed to avoid residual confounding.

Post-baseline concomittant drugs

- The underlying DAG can be very complicated, and the risk of residual post-baseline confounding can be high.



- $M_t(0,1)$: corticoid use at time $t = 0, 3, 6, \ldots$ months;
  L_t: post-baseline confounders at time t, e.g. psoriatic severity.
- A Cox model adjusting only for corticoid use as a time-varying variable will ignore other important confounders.

Censoring and truncation by death

- Yiu et al (2018): patients who switched from the non-biologic therapy cohort to start a biologic contributed follow-up time to both cohorts.
  - It is a little unclear to me how the correlation is then taken into account.
- Yiu et al (2018) and Penso et al (2018) censor patients who died.
  - This violates the non-informative censoring assumption in the Cox model.
  - Penso et al (2018) additionally consider a competing risk model. This is deemed as more relevant.

Conclusions

- Evaluating infection risk of different treatment options in biologic is a challenging question.
- Careful consideration is required in the design and conduct of the study to ensure adequate statistical power and to minimise the bias.
- More advanced causal inference methods should be used to strengthen the robustness of the findings.