Response to: 'Correspondence on 'Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19- associated cytokine storm syndrome: results of the CHIC study" by Klopfenstein *et al*

In rheumatology and beyond, clinical trial researchers often interpret observed treatment contrasts (between two trial arms) as if these contrasts are constant across the entire spectrum of disease severity. While understandable, researchers, regulators and society usually aim at finding *one* effective treatment for the *whole* disease, a constant effect interpretation is a simplification of the truth. Often, effective treatments have relatively most effect when applied in the sickest. Benefit may be less impressive when applied in those with milder disease: effect modification or (statistical) interaction. Klopfenstein *et al* touch on this rather ubiquitous but often ignored phenomenon, by demonstrating that the treatment contrast of tocilizumab versus control in trials with patients with COVID-19 is not constant but depends on the trial patients' baseline severity, here expressed as the risk to die in the control arms of the trials.[1]

One may speculate why this common principle is so often ignored in medicine. A likely explanation is that we usually select the most severe patients for our drug trials, by applying stringent inclusion criteria for disease activity (figure 1). By doing so, we exploit the principle of constant treatment contrast in our advantage. Extrapolating similar beneficial treatment effects found in the sickest to those with milder disease, however, is spurious, because it ignores the possibility of effect modification. Many have pointed to this omission that is so paramount in rheumatology. Think of rheumatoid arthritis (RA): we know very well how to treat our most active patients with RA, even though they constitute a minority in our clinical practice, but lack good clinical evidence (trials) about treating the milder cases, which are far more prevalent.

Klopfenstein *et al* have now elegantly demonstrated that ignoring effect modification may lead to confusion and delays in the approval and application of effective medicines for a new disease like COVID-19.[1] Indications for effect modification can also be found in the famous Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, in which *dexamethasone* appeared most effective in those who needed oxygen supplementation at baseline, while the beneficial effect was only marginally significant for the whole trial population.[2]

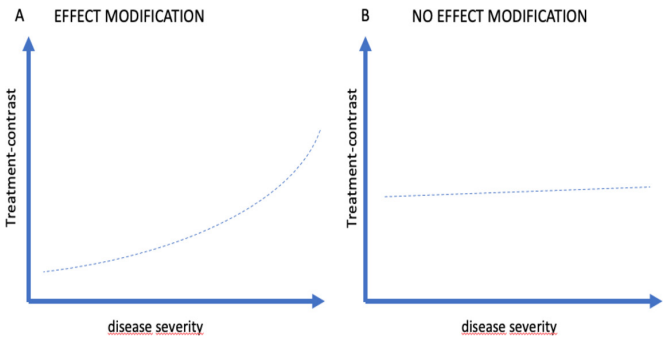

Figure 1 Schematic representation of treatment effects. (A) Effect modification. (B) No effect modification.

Until the day of today, up to 1 year after we had published the first favourable study in the medical literature and the lay press,[3 4] confusion remains among experts and guideline developers about whether tocilizumab is effective or not in patients with COVID-19. Klopfenstein *et al* have provided an insightful answer: Tocilizumab is indeed effective, but only in patients with high baseline risk. They remind us eloquently of the fact that for obtaining good clinical evidence more is needed than only large randomised trials.

Robert BM Landewé [1,2] **Sofia Ramiro** [1,3] **Rémy L M Mostard**[4]

[1]Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands
[2]Amsterdam Rheumatology Center, AMC, Amsterdam, The Netherlands
[3]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Pulmonology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands

Correspondence to Professor Robert BM Landewé, Amsterdam Rheumatology Center, AMC, 1105 AZ Amsterdam, Netherlands; landewe@rlandewe.nl

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ORCID iDs
Robert BM Landewé http://orcid.org/0000-0002-0577-6620
Sofia Ramiro http://orcid.org/0000-0002-8899-9087

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