Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among patients with COVID-19, should tofacitinib be used for treatment?

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RECOMMENDATION

We suggest against the use of tofacitinib among hospitalized COVID-19 patients. *(Low quality of evidence; Weak recommendation)*

Consensus Issues

The recommendation against the use of tofacitinib among hospitalized patients with COVID-19 was mainly due to the drug's safety issues. Although the study showed that there was benefit in reducing death or respiratory failure, particularly among patients on low-flow supplemental oxygen, patients who received tofacitinib were three times more likely to experience adverse events leading to treatment discontinuation. Furthermore, the US FDA and Health Canada issued safety alert on the use of tofacitinib due to increased risk of serious cardiovascular-related events (heart attack, stroke), cancer (lymphoma, lung cancer), thrombosis and death.

Key Findings

There is one (1) randomized controlled trial (RCT) that investigated the effect of tofacitinib compared to placebo as treatment for patients with COVID-19. Patients treated with tofacitinib had a significant reduction in death or respiratory failure. Tofacitinib did not show significant effect in all-cause mortality, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), cure (defined as resolution of fever, cough, or need for ventilatory/oxygen support), length of hospitalization, length of ICU stay, and duration of mechanical ventilation. There was no significant increase in serious adverse events and adverse events between the tofacitinib and placebo group. However, there was a significant increase in adverse events leading to treatment discontinuation for patients given tofacitinib compared to placebo, with increase in transaminase levels and lymphopenia being the most commonly reported adverse events. The very serious imprecision due to the limited number of events contributed to the downgrading of evidence to a low certainty of evidence.

Introduction

Tofacitinib is a Janus kinase (JAK) inhibitor that is used for adults with rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, and for children with juvenile idiopathic arthritis. JAK pathways are involved in inflammatory gene expression and perpetuates an inflammatory cycle. Inhibition of JAK leads to an anti-inflammatory effect through decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines.[1] Mortality in COVID-19 infection has been associated with a cytokine storm characterized by excessive production of proinflammatory cytokines.[2] The action of tofacitinib in inhibiting cytokine production provide the rationale for evaluating its use in COVID-19.

Review Methods

A systematic search was done using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and tofacitinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only RCTs that compared tofacitinib against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of tofacitinib. Subgroup analysis by disease severity, oxygen requirement, and age was planned.

Results

The initial search yielded 86 articles. After review of search output, one (1) RCT was retrieved with a total of 289 participants that evaluated the use of tofacitinib in the treatment of hospitalized COVID-19 patients. This RCT was also included in the COVID-NMA Living Data.[3] Patients on non-invasive/invasive mechanical ventilation or ECMO, with history of thrombosis or current thrombosis, with known suppression or those with current cancer were excluded from the study. The treatment group received a dose of tofacitinib 10mg twice daily for 14 days or until hospital discharge, whichever was earlier. A reduced regimen of 5mg tofacitinib twice daily was administered for patients with estimated glomerular filtration rate of <50 mL/min/1.73m^2, moderate hepatic impairment or concomitant use of strong CYP3A4 or CYP2C1 inhibitors. The control group received placebo. All study participants received standard of care, including glucocorticoids, antibiotics, anticoagulants, and anti-viral agents. Concomitant use of other JAK inhibitors, biologic agents, immunosuppressants, interleukin-1 inhibitors, interleukin-6 inhibitors or CYP450 inducers were prohibited. Outcomes measured during the 28-day follow-up included death or respiratory failure, all-cause mortality, need for mechanical ventilation or ECMO, duration of hospital stay, duration of ICU stay, cure (defined as resolution of fever, cough, no use of ventilatory or oxygen support), hospital discharge, and serious adverse events. The characteristics of included studies are summarized in Appendix 3.

The overall quality of evidence was rated low because of very serious imprecision due to the small number of events and wide confidence intervals. Appraisal of study quality showed no serious risk of bias in the included study. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Result of the RCT showed significant reduction in death or respiratory failure among patients who received tofacitinib compared to placebo (RR 0.62, 95% CI 0.40-0.96). Subgroup analysis by severity showed trend towards benefit for patients not receiving supplemental oxygen (RR 0.71, 95% CI 0.21-2.00) and high-flow supplemental oxygen (RR 0.62, 95% CI 0.15-1.79); however, results did not reach statistical significance. There was significant benefit for patients on low-flow supplemental oxygen (RR 0.59, 95% CI 0.33-0.97).
Point estimates also showed trend towards benefit for all-cause mortality (RR 0.50, 95% CI 0.16-1.64) and need for mechanical ventilation or ECMO (RR 0.25, 95% CI 0.03-2.23); however, the wide confidence intervals preclude definite conclusions to be made.

There was no significant difference in cure, defined as resolution of fever, cough or need for ventilatory/oxygen support (RR 1.03, 95% CI 0.95-1.10). There was also no significant difference in median length of hospitalization (tofacitinib group 5.5 days, 95% CI 3.0-8.25; placebo group 6.0 days, 95% CI 3.0-11.0; subdistribution hazard ratio 1.18, 95% CI 0.94-1.48) and median length of ICU stay (tofacitinib group 5.0 days, 95% CI 3.0-11.0; placebo group 5.0 days, 95% CI 2.0-11.5; subdistribution hazard ratio 1.11, 95% CI 0.72-1.70), and duration of mechanical ventilation (median difference 1.00 days, 95% CI -7.0 to 7.0).

Adverse events

In terms of serious adverse events, the point estimate shows trend towards harm among those given tofacitinib compared to placebo. However, the wide confidence interval precludes definite conclusions to be made (RR 1.18, 95% CI 0.64-2.15). Among the serious adverse events of special interest, deep-vein thrombosis, acute myocardial infarction, ventricular tachycardia, and myocarditis occurred in 1 patient each in the tofacitinib group. In the placebo group, hemorrhagic stroke and cardiogenic shock occurred in 1 patient each.

The point estimate for adverse events also shows trend towards harm for tofacitinib; however, results were not statistically significant (RR 1.16, 95% CI 0.77-1.75). The most common adverse events were increase in aminotransferase levels, acute kidney injury, anemia, hyperglycemia, and lymphopenia. There was a significant increase in adverse events leading to treatment discontinuation in the tofacitinib group compared to the placebo group (RR 3.2, 95% CI 1.2-8.5). Increase in transaminase levels and lymphopenia were the most commonly reported adverse events leading to treatment discontinuation.

Recommendations from Other Groups

Table 1. Summary of Recommendations from other Groups

Regulatory Agency	Recommendation
Infectious Diseases Society of America (IDSA) (as of October 1, 2021)	Suggests the use of tofacitinib rather than no tofacitinib among hospitalized adults with severe COVID-19 (severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device, but not on non-invasive or invasive mechanical ventilation *(Low certainty of evidence; Conditional recommendation).* Patients treated with tofacitinib should be on at least prophylactic dose anticoagulant, and that these patients should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19.[6]
National Institutes of Health (NIH) COVID-19 Guidelines (as of October 7, 2021)	Recommends tofacitinib for hospitalized COVID-19 patients as an alternative to baricitinib only when baricitinib is not available or not feasible to use *(Moderate recommendation).[*7]
Australian Guidelines for COVID-19 (as of September 29, 2021)	Does not recommend the use of tofacitinib for the treatment of COVID-19 outside of randomized trials *(Low certainty of evidence).[*8]

Surviving Sepsis Campaign Guidelines on COVID-19 (as of January 29, 2021)	No recommendation on tofacitinib for treatment of COVID-19.[9]
World Health Organization (WHO) (as of September 24, 2021)	No recommendation on tofacitinib for treatment of COVID-19.[10]

Research Gaps

There are five (5) studies in various clinical trial registries, of which 1 was withdrawn so that the investigators can pursue other COVID-19 related research. This review will be updated as soon as full results from these trials become available.

References

[1] Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB, et al. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2016;34(2):318-28.

[2] Ragab D, Eldin HS, Mohamed T, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;11:1446.

[3] Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-15.

[4] UptoDate. Tofacitinib: Drug Information. Available from https://www.uptodate.com/contents/tofacitinib-drug-information. Accessed 11 September 2021.

[5] Watsons. Xeljanz Tofacitinib. Available form https://www.watsons.com.ph/tofacitinib-11mg-1-tablet/p/BP_50028739. Accessed 11 September 2021.

[6] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.1.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 22 September 2021.

[7] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 22 September 2021

[8] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.1. Available from https://app.magicapp.org/#/guideline/5596. Accessed 22 September 2021.

[9] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 6 July 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed 22 September 2021.

[10] Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update, Accessed 22 September 2021 https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=9)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)				• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity
Benefits	Large	Moderate (4)	Small (3)	Uncertain (2)		• Significant reduction in death or respiratory failure (RR 0.62, 95% CI 0.40-0.96) • Significant benefit for patients on low-flow supplemental oxygen (RR 0.59, 95% CI 0.33-0.97)
Harm	Large (7)	Small (1)	Uncertain (1)			• Trend towards harm among those given tofacitinib compared to placebo, but wide confidence interval precludes definite conclusions to be made (RR 1.18, 95% CI 0.64-2.15) • Significant increase in adverse events leading to treatment discontinuation (RR 3.2, 95% CI 1.2-8.5)
Certainty of Evidence	High	Moderate	Low (8)	Very low (1)		• Low because of very serious imprecision due to the small number of events and wide confidence intervals
Balance of effects	Favors drug (3)	Does not favor drug (3)	Uncertain (3)			• There was variability prior to the panel discussion • However, the consensus panel eventually decided that the potential harm of giving tofacitinib outweighed its potential benefits
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability		

Resources Required	Uncertain	Large cost (4)	Moderate Cost (5)	Negligible cost	Moderate savings	Large savings	• Php 22,799.00 per 14 day treatment course
Certainty of evidence of required resources	No included studies	Very low (1)	Low (4)	Moderate (2)	High (2)	• Based on published online rates of a Philippine drug store website	
Cost effectiveness	No included studies (8)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention		• None of the included trials assessed cost effectiveness.	
Equity	Uncertain (6)	Reduced (2)	Probably no impact	Increased (1)			
Acceptability	Uncertain (9)	No	Yes				
Feasibility	Uncertain (5)	No	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (tofacitinib OR tofacitinib[supplementary concept, Mesh])	September 11, 2021 11:00AM	44	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (tofacitinib) Filters: March 26, 2021 to August 28, 2021	September 11, 2021 11:15 AM	11	1
COVID-NMA Initiative	Tofacitinib	September 11, 2021 11:25 AM	1	1
Google Scholar	Tofacitinib AND COVID19 AND randomized trial	September 11, 2021 11:27 AM	30	1
ClinicalTrials.gov	Tofacitinib and COVID19	September 11, 2021 11:35 AM	6	4
Chinese Clinical Trial Registry	Tofacitinib	September 11, 2021 11:45 AM	11	0
EU Clinical Trials Register	Tofacitinib	September 11, 2021 11:50 AM	2	1
Republic of Korea - Clinical Research Information Service	Tofacitinib	September 11, 2021 11:52 AM	0	0

Japan Primary Registries Network/ NIPH Clinical Trials Search	Tofacitinib	September 11, 2021 11:53 AM	25	0
CenterWatch	Tofacitinib and COVID	September 11, 2021 11:58 AM	1	1
WHO database COVID-19 studies	Tofacitinib	September 11, 2021 12:00 PM	8	2
chinaxiv.org	Tofacitinib	September 11, 2021 12:10 PM	0	0
Medrxiv.org	Tofacitinib and COVID	September 11, 2021 12:12 PM	29	0
Biorxiv.org	Tofacitinib and COVID	September 11, 2021 12:20 PM	16	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia *Guimaraes et al. 2021 (Brazil)*	N = 289 18 years and older with: ● Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR ● Evidence of COVID-19 pneumonia assessed by radiographic imaging (CT or radiography) ● Hospitalized for less than 72 hours Exclusion criteria: ● Use of noninvasive or invasive mechanical ventilation or ECMO ● History of thrombosis or current thrombosis ● Known immunosuppression ● Current cancer <u>Duration of follow-up:</u> Up to 28 days after discharge	Experimental: Tofacitinib 10mg twice daily for 14 days or until hospital discharge (N = 144) Control: Placebo (N = 145)	Primary: Death or respiratory failure until Day 28 Secondary: all-cause mortality, scores of the NIAID ordinal scale of disease severity at day 14 and 28, need for mechanical ventilation or ECMO at day 14 and 28, duration of stay in the hospital, duration of stay in the ICU, cure (resolution of fever, cough, no use of ventilatory or oxygen support), hospital discharge at day 14 and 28, serious adverse events	Randomized, Double-blind, Placebo-controlled, Parallel-design Trial

Appendix 4. Study Appraisal

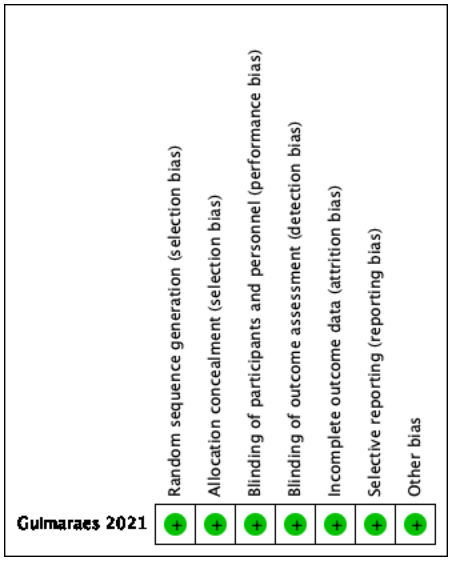

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan-Lim, MD, MSc
Question: Tofacitinib compared to Placebo/Standard Care for COVID-19
Setting: Hospital setting
Bibliography: Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-15.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tofacitinib	Placebo/Standard Care	Relative (95% CI)	Absolute (95% CI)		
Death or respiratory failure (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	26/144 (18.1%)	42/145 (29.0%)	**RR 0.63** (0.41 to 0.97)	**107 fewer per 1,000** (from 171 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
All-cause mortality (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	4/144 (2.8%)	8/145 (5.5%)	**RR 0.49** (0.15 to 1.63)	**28 fewer per 1,000** (from 47 fewer to 35 more)	⨁⨁◯◯ LOW	CRITICAL
Progression to mechanical ventilation or ECMO (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	1/144 (0.7%)	4/145 (2.8%)	**RR 0.25** (0.03 to 2.23)	**21 fewer per 1,000** (from 27 fewer to 34 more)	⨁⨁◯◯ LOW	CRITICAL
Cure (resolution of fever, cough, or need for ventilatory/oxygen support) (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	134/144 (93.1%)	132/145 (91.0%)	**RR 1.03** (0.95 to 1.10)	**27 more per 1,000** (from 46 fewer to 91 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital discharge (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	134/144 (93.1%)	129/145 (89.0%)	**RR 1.05** (0.97 to 1.13)	**44 more per 1,000** (from 27 fewer to 116 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	20/142 (14.1%)	17/142 (12.0%)	**RR 1.18** (0.64 to 2.15)	**22 more per 1,000** (from 43 fewer to 138 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events leading to treatment discontinuation												

1	randomised trials	not serious	not serious	not serious	serious [c]	none	16/142 (11.3%)	5/142 (3.5%)	**RR 3.2** (1.2 to 8.5)	**77 more per 1,000** (from 7 more to 264 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Upper boundary of 95% CI crosses threshold for meaningful effect
b. Wide confidence interval, small number of events
c. Small number of events

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Tofacitinib for Treatment of Moderate COVID-19 NCT04415151	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging, and hospitalized	Experimental: Tofacitinib 10mg PO BID until return to their clinical baseline and then at 5mg PO BID for a total of 14 days Control: Placebo	Disease Severity (Time Frame: 14 days)	Randomized, double blinded, placebo-controlled study
2. Safety and Efficacy of Tofacitinib in Hospitalized Participants With COVID-19 Pneumonia Who Are Receiving Standard of Care Therapy NCT04412252 *Withdrawn to pursue other COVID-19 research*	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging	Experimental: Tofacitinib 10mg twice daily for 14 days Control: Placebo	Clinical status using ordinal scale (Time Frame: Day 28)	Randomized, Double-blind, Placebo-controlled, Parallel-group study
3. TOFAcitinib Plus Hydroxycloroquine vs Hydroxycloroquine in Patients With COVID-19 Interstitial Pneumonia (TOFACoV-2) NCT04390061	18 to 65 years old with SARS-CoV2 infection diagnosed by RT-PCR, hospital admission from less than 24 hours, P/F ratio >150 mmHg	Experimental: Tofacitinib 10mg twice daily + hydroxychloroquine 200mg thrice daily for 14 days Control: hydroxychloroquine 200mg thrice daily for 14 days	Prevention of severe Respiratory Failure requiring mechanical ventilation (Time Frame: 14 days)	Randomized, parallel assignment open label trial
4. Evaluation of use and right time identification to initiate Tofacitinib use in the treatment of moderate-severe COVID-19 infection CTRI/2021/06/034162	18 years and older with signs and symptoms consistent with COVID-19 infection confirmed with rapid antigen test (RAT) or RT- PCR and hospitalised with moderate or severe COVID-19 illness	Experimental: Tofacitinib 10mg BID on top of Standard Care for 10 days Control: Standard Care	All-cause mortality up to 28 days of follow-up	Open label randomised, controlled trial
5. Effectiveness evaluation of Tofacitinib plus Remdesivir in comparison with Remdesivir in the treatment of adult patients with severe COVID-19 A randomized double-blind placebo-included clinical trial IRCT20200329046892N2	All patients with severe COVID-19 admitted to the ICU of Razi Hospital in Rasht from March to June 2021	Experimental: Tofacitinib oral tablet 10mg daily + remdesivir IV 100mg daily for 14 days or hospital discharge Control: Placebo oral tablet daily + Remdesivir IV 100mg daily for 14 days or hospital discharge	The time required to improve clinical symptoms and paraclinical measures within 14 days of starting treatment	Double-blind, randomized clinical trial with parallel control group