Special article

Anti-IL-6 receptor antibody treatment for severe COVID-19 and the potential implication of IL-6 gene polymorphisms in novel coronavirus pneumonia

Tratamiento con anticuerpos anti-receptor de IL-6 para COVID-19 grave y la posible implicación de polimorfismos del gen IL-6 en la nueva neumonía por coronavirus

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Despite the rapid global increase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there is currently no effective treatment for patients who have developed severe coronavirus disease 2019 (COVID-19). These severe COVID-19 cases are marked with excess cytokine production and a higher mortality rate. Our previous analysis confirmed that an elevated level of interleukin-6 (IL-6) and C-reactive protein (CRP) are strongly associated with COVID-19 progression. 1,2 Thus, it is reasonable to suggest that the inhibition of IL-6 signaling cascade may effectively treat patients with severe SARS-CoV-2 infection. Another potential consideration regarding disease progression is the role of IL-6 gene polymorphisms. The two most extensively studied IL-6 gene promoter polymorphisms, −174G/C (rs1800795) and −572C/G (rs1800797), have been shown to affect both the transcription and secretion level of IL-6. 3 Although the role of such polymorphisms have not been studied among COVID-19 patients specifically, it has been demonstrated in other infectious pneumonias.

In this article, we present a systematic review and meta-analysis on the efficacy of anti-IL-6 receptor (anti-IL-6R) antibody in neutralizing IL-6 by evaluating the reduction of the C-reactive protein (CRP) inflammatory marker, clinical outcomes, and the adverse events among severe COVID-19-infected patients. Additionally, a meta-analysis was also performed to estimate the association between IL-6 gene polymorphism with predisposition as well as disease severity of pneumonia.

All meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. 4 Records were identified through electronic databases dated up to May 2020 with search terms such as “COVID-19” “SARS-CoV-2”, “IL-6”, “anti-IL-6R”, “Tocilizumab (TCZ)”, “pneumonia” (See Supplementary material). No language restrictions were applied. For TCZ treatment, studies with case-control design evaluating clinical outcomes (i.e., mortality rate, ICU admission, the requirement of mechanical ventilation, and the number of discharged patients) and its adverse events were included. Whereas, for IL-6 gene polymorphisms, studies were included on the basis of the following criteria: (1) aims to evaluate the association between IL-6 gene polymorphisms with predisposition to pneumonia; (2) conducted with a case-control design; and (3) evaluates IL-6 gene polymorphisms in pneumonia patients with or without severe condition (i.e., extra pulmonary bacterial dissemination, sepsis, and multiple organ dysfunction syndrome (MODS)).

Meta-analysis for each gene polymorphism was performed for two or more studies. Genotypic frequency of IL-6 gene polymorphism was tested for deviation from the Hardy–Weinberg equilibrium (HWE) in the control subjects. The associations between IL-6 gene polymorphism with predisposition to pneumonia or severity of pneumonia were calculated by pooled odds ratio (OR) and 95% confidence interval (CI). The Z test was used to evaluate the significance of the pooled effect size. Study heterogeneity was evaluated using Q test and I2 statistic. A significant Q-statistic (p < 0.10) indicated heterogeneity across studies, with substantial heterogeneity indicated by an I2 value over 50%.
fixed-effect model (FEM) was used in the absence of heterogeneity, whilst the random-effect model (REM) was implemented if heterogeneity was present. A funnel plot and Begg’s test were used to investigate the publication bias if the pooled effect size consisted of 10 or more studies. The value of 0.05 was indicative of the statistical significance. The Newcastle–Ottawa scale (NOS) was used to assess the study quality, in which a score ≥ 7 is considered a good study.5–10

Nine case reports/case-series were included for the analysis on anti-IL-6R antibody treatment (summarized in Table 1) with a total sample of $n = 66$ patients. A large proportion of the samples (89%) were male, with ages ranging from 42 to 73 years old.10–18 All patients developed severe COVID-19, marked by acute respiratory distress syndrome (ARDS) during admission, and more than half of studies reported the use of mechanical ventilators. Hypertension was the most common co-morbidity observed in patients with SARS-CoV-2 infection, followed by diabetes mellitus (DM), cerebrovascular disease, cardiovascular disease (CVD), and chronic kidney disease (CKD). Eight of the studies administered TCZ treatment,11–18 while one utilized Siltuximab.19 One to three times injection of anti-IL-6R antibody was mainly given during the onset of ARDS,11,13–15,18 while the rest were administered several days after the admission/ARDS onset12,15,18,19 or depending on the level of IL-6 or CRP.17 Several additional treatments were given in

### Table 1

| Characteristics | Michot et al. | Zhang et al. | De Luna et al. | Cellina et al. | Di Giambenedetto et al. | Radbel et al. | Gritti et al. | Xu et al. | Luo et al. |
|-----------------|---------------|--------------|----------------|-----------------|-------------------------|---------------|--------------|-----------|-----------|
| **Location**    | France        | China        | France         | Italy           | Italy                   | USA           | Italy        | China     | China     |
| **Study type**  | Case report   | Case report  | Case report    | Case report     | Case report             | Case report   | Retrospective case-series | Retrospective case-series | Retrospective case-series |
| **Number of cases** | 1            | 1            | 1              | 1               | 3                       | 2             | 1            | 21        | 73        |
| **Age [years]** | 42            | 60           | 45             | 64              | 56.33 [mean]            | 54.5 [mean]   | 64 [median]  | 56.8 [mean] | 73 [median] |
| **Males, %**    | 100 ARDS      | 100 ARDS     | 100 ARDS       | 100 ARDS        | 100 ARDS                | 50 ARDS       | 85.7 ARDS   | 85.7 ARDS | 80 ARDS |
| **Major clinical feature** | No           | No           | No             | Yes             | No                      | No            | No           | Yes       | Yes (15%) |
| **Onset of ARDS** | 7-days after admission/2-days after SARS-CoV-2 was confirmed | 15-days after admission/12-days after SARS-CoV-2 was confirmed | 1 day after admission | 5-days after admission | 8-days after admission (patient 1) | At admission (patient 2) | 2-days after admission (patient 3) | Yes | Yes |
| **Mechanical ventilation** | No            | No           | Multiple myeloma | SCF             | No                      | Hypertension   |
| **Co-morbidities** | Renal cell carcinoma | Multiple myeloma | SCD            | NR              | DM, rheumatoid arthritis, aplastic anemia |
| **Anti-IL-6R treatment** | TCZ At the onset of ARDS | TCZ At the onset of ARDS | TCZ At the onset of ARDS | TCZ At the onset of ARDS | TCZ At the onset of ARDS | Siltuximab 3-Days after admission [median] | TCZ NR | TCZ Depending on the level of IL-6 or CRP |
| **Dose** | 8 mg/kg IV (2 times, 8 h interval) | 8 mg/kg IV (1 time) | 8 mg/kg IV (2 times, 12 h interval) | 8 mg/kg IV (2 or 3 times, 12 h interval for the second dose or 24/26 h for the third dose) | 400 mg IV (1 time, patient 1) | 560 mg IV and 700 mg IV (2 times, 2 days interval, patient 2) | 11 mg/kg IV (1 time) | 400 mg IV (1 time) | 80–600 mg IV (≥2 times) |
| **Characteristics** | Michot et al. | Zhang et al. | De Luna et al. | Cellina et al. | Di Giambenedetto et al. | Lopinavir/Ritonavir | HCQ | HCQ, azithromycin, NE (vasopressor, steroids) | Lopinavir, Methylprednisolone | Methylprednisolone |
| **Co-treatment** | Ceftriaxone, Piperacillin, tazobactam, Lopinavir/Ritonavir | Moxifloxacin, Umifenovir | Amoxicillin-clavulanic acid | HCQ | NR | NR | NR | Lopinavir, Methylprednisolone | Methylprednisolone |
Table 1 (Continued)

| Evaluation time (for CRP level) | Day-4 post-treatment | Day-7/14 post-treatment | % Reduction of CRP from baseline (before treatment) | Day-1 post-treatment | Day-2/3/10 post-treatment | Day-1/2/3 post-treatment | Day-5 post-treatment | Day-1/3/5 post-treatment | Day-1/2/3/4/5/6/7 post-treatment |
|--------------------------------|-----------------------|-------------------------|-------------------------------------------------|----------------------|--------------------------|--------------------------|------------------------|--------------------------|----------------------------------|
| % Reduction of IL-6 level      | 85.33                 | 10/77.9                 | NR                                              | 71.42                | -10.16/12.46/66.23       | -78.63                   | 49.20/85.86/96.37       | 64.89/73.93/86.65/92.83/82.42/58.75/88.64 |
| ARDS                          | nea                 |                         | can                                             |                      |                          |                          |                        |                          |
| (Supp. adverse                 |                        |                         | effects                                          |                      |                          |                          |                        |                          |
| IL-6 level                    | NR                   | 82.88% reduction after 10-days of TCZ treatment | NR                                              | NR                   | NR                       | IL-6 level tended to spike and then decreased following TCZ treatment | NR                   |
| Chest CT                      | Improvement after 4-days TCZ treatment | Improvement after 12-days TCZ treatment | NR                                              | Improvement after 7-days TCZ treatment | Improvement after 2 or 3-days TCZ treatment | Generally improved (afaebile and decreased oxygen consumption) | Generally improved (released from mechanical ventilation) | Died (both patients progressed to secondary hemophagocytic lymphohistioctyous (sHLH).) | Generally improved |
| Clinical outcome              | Generally improved (afaebile and decreased oxygen consumption) Gradually recovered after TCZ treatment Generally improved after 1-day TCZ treatment | Generally improved (afaebile and improvement of PaO2-to-FIO2 ratio) | Generally improved (released from mechanical ventilation) | 33% of patients were clinically improved (released from mechanical ventilation) | Generally improved | Generally improved (afaebile and improvement of the peripheral oxygen saturation) |

ARDS, acute respiratory distress syndrome; CVD, cardiovascular disease; CKD, chronic kidney disease; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HCQ, hydroxychloroquine; IV, intravenous; NR, not reported; SCD, sickle cell disease. TCZ, Tocilizumab.

Fig. 1. Pooled reduction of C-Reactive Protein following administration of anti-IL-6R antibody in severe pneumonia. Figure shows mean ± standard error of the mean. n = 2–4 studies per group.

clinical presentation24 (Table 2). No statistical significance was observed between the pooled mortality rates of the TCZ and standard treatment (STD) groups, which may be due to the heterogeneity between studies. However, it can be noted that relative to STD treatment, TCZ treatment was marginally associated with lower mortality rate (HR = 0.39, 95%CI 0.01–0.77, p = 0.09, Fig. 2A; OR = 0.30, 95%CI 0.08–1.10, p = 0.07, Fig. 2B). In a study conducted by Sciascia et al.,25 TCZ treatment was shown to increase the likelihood of survival among severe COVID-19 patients (Table 2).

This analysis also showed that invasive mechanical ventilation (IMV) was required less in the TCZ group (OR = 0.10, 95%CI 0.01–0.77, p = 0.03, Fig. 2C). No statistical difference was observed in terms of ICU admissions, the number of discharged patients, and the adverse effects of treatment (bacteremia and an elevated level of AST/ALT) between the two groups (Fig. 2D, E, Supplemental Fig. 1, respectively). Interestingly, however, Morena et al.26 demonstrated that 67% of patients administered with TCZ showed an improvement in their clinical severity class. Thus, the administration of TCZ seems beneficial in lowering the mortality rate and increased favorable clinical outcomes in patients with severe SARS-CoV-2 infection. However, additional data are still required to understand the effect of TCZ in treating patients with severe and critically ill COVID-19.

For the analysis on IL-6 gene polymorphisms and pneumonia, 24 articles were found using the aforementioned search strategy. Irrelevant articles were subsequently excluded, leaving a total of 11 eligible studies. The total sample included for analysis were 3958 cases and 3671 controls; 717 cases and 579 controls for IL-6 –174G/C and –572G/G polymorphisms, respectively27–30 (Supp. Refs. 1–7). To assess the association between IL-6 –174G/C with pneumonia severity, 671 severe and 2910 non-severe cases were examined29 (Supp. Ref. 3.6) The characteristics of the included studies are shown in Table 2. All but four of the studies30 (Supp. Ref. 2.3,5) did not comply with the HWE (p < 0.05). Overall, a lack of association between IL-6 –174G/C and –572G/G polymor-
| Author         | Location | No. of TCZ/STD treated patients | TCZ eligibility criteria                                                                 | Therapy                                                                 | Outcome at days | Survival rate (HR, 95% CI) | Mortality | Required IMV | ICU admission | Discharge | Adverse effect* |
|----------------|----------|---------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------|----------------------------|------------|--------------|---------------|-----------|----------------|
| Campochiaro et al. | Italy    | 32/33                           | **2X Positive RT-PCR of SARS-CoV-2 on nasopharyngeal swab; hyper-inflammation (CRP ≥100 mg/L or r ferritin ≥900 ng/ml); severe respiratory involvement (chest X-ray/CT, SaO₂ < 92%, PaO₂/FiO₂ < 300 mmHg)** | STD: HCQ, lopinavir/ritonavir, ceftriaxone, azithromycin, anti-coagulation prophylaxis TCZ: STD + TCZ 400 mg IV (1 time, 24 h interval for the second dose) | 28              | HR for death 0.44, 95% CI 0.167–1.184, p = 0.122 | 5/32       | 0/32         | 1/33          | –         | 20/32/16/33   |
| Capra et al.    | Italy    | 62/23                           | Confirmed SARS-CoV-2, and one of the following criteria: RR > 30 breaths/min, SpO₂ < 93%, PaO₂/FiO₂ < 300 mmHg; severe respiratory involvement by chest X-ray | STD: HCQ, lopinavir, ritonavir TCZ: STD + TCZ 400 mg IV or 324 mg SC (1 time) | 35              | HR for death 0.035, 95% CI 0.004–0.347, p = 0.004 | 2/62       | –            | 11/23         | –         | 23/62/8/23    |
| Colaneri et al. | Italy    | 21/91                           | Confirmed SARS-CoV-2; CRP > 5 mg/dl, PCT < 0.5 ng/mL, PaO₂/FiO₂ < 300; ALT > 500 U/L | STD: HCQ, azithromycin, prophylactic dose of low weight heparin, and methylprednisolone TCZ: STD + TCZ 400 mg IV | 7               | –                          | 5/21       | 19/91        | –             | –         | 0/21b/0/91    |
| Klopfensteina et al. | France  | 20/25                           | Confirmed SARS-CoV-2; failure of standard treatment, oxygen therapy ≥ 5 l/min, >25% of lung damages on chest computed tomography (CT) scan, and ≥ 2 parameters of inflammation (high level of ferritin, CRP, D-dimers, lymphopenia, and LDH) | STD: HCQ, lopinavir-ritonavir, antibiotics, corticosteroids TCZ: STD + TCZ (1 or 2 doses) | 11              | –                          | 5/20       | 12/25        | 0/20          | 8/25      | 0/20/11/25/11/20/11/25 |
| Author          | Location  | No. of patients | TCZ eligibility criteria          | Therapy                                                                 | Outcome (HR 95% CI)                  | Adverse effect |
|-----------------|-----------|-----------------|-----------------------------------|-------------------------------------------------------------------------|--------------------------------------|---------------|
| Sciascia et al. | Italy     | 56              | Confirmed SARS-CoV-2, SpO₂ < 93%, PaO₂/FiO₂ < 300 mmHg, IL-6 plasma level > 40 pg/mL | TCZ 8 mg/kg IV or 324 mg SC (1 or 2 doses)                              | Survival rate according to D-dimer levels, HR 2.2 (95% CI 1.3–6.7), p < 0.05               | No adverse effect reported |
| Morena et al.   | Italy     | 51              | Confirmed SARS-CoV-2, age ≥ 18 years, RR ≥ 30 min⁻¹, SpO₂ < 93%, PaO₂/FiO₂ < 250 mmHg, IL-6 plasma level > 40 pg/mL | TCZ 400 mg IV or 8 mg/kg (1 or 2 doses) (275 RBU)                       | Survival rate according to severity of the disease, HR 67% (95% CI 56–68)                  | Increased AST/ALT (29%), Bacteremia (27%)         |
| Qurenn et al.   | Italy     | 42/69           | Confirmed SARS-CoV-2, IL-6 level of CRP and IL-6 | STD: antivirals, antimalarials, glucocorticoids, antibiotics, LMWH       | Survival rate according to severity of the disease, HR 2.2 (95% CI 1.3–6.7), p < 0.05   | No adverse effect was reported |

TCZ, Tocilizumab; STD, Standard treatment; *adverse effects including secondary infection or severe hepatic injury; ATB, antibiotic. All doses must be converted to mEq/L units. CT, computerized tomography; PCT, procalcitonin; RT-PCR, reverse transcription polymerase chain reaction; SC, subcutaneous; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
phisms with pneumonia predisposition was observed in all genetic models (Table 3). Additionally, results remained insignificant following subgroup analysis based on ethnicity and age (data not shown).

Interestingly however, we found that IL-6 −174G/C polymorphism was significantly associated with the severity of pneumonia (C vs. G: OR: 1.33, 95% CI: 1.04−1.69, p = 0.019, Fig. 3A; particularly in the Caucasian population: OR: 1.15, 95% CI: 1.00−1.33, p = 0.049; CC+GC vs. GG: OR: 1.20, 95% CI: 1.07−1.53, p = 0.006, Fig. 3B; CC vs. GG: OR: 1.55, 95% CI: 1.18−2.03, p = 0.001, Fig. 3C, Table 3). In line with our results, Feng et al. [Supp. Ref. 8] observed that carriers of the IL-6 −174G/C had a 2.42-fold higher risk for pneumonia-induced septic shock, thereby implying a higher tendency of severe pneumonia in patients harboring the IL-6 −174C. Indeed, the CC genotype has been correlated with significantly higher IL-6 levels [Supp. Ref. 3,9]. Moreover, it has been shown that the haplotype spanning from −1363 to +4835 from the transcription start site of IL-6 conferred susceptibility to acute lung injury (ALI) [Supp. Ref. 10] (Table 4).

Tocilizumab, Sarilumab, or Siltuximab are humanized recombinant monoclonal antibodies that inhibit IL-6 signal transduction of IL-6 by binding with the soluble and membrane IL-6R, sIL-6R and mIL-6R, respectively. So far, anti-IL-6R antibody is mainly used to treat rheumatoid arthritis patients with favorable safety profile.11 Since these agents are immunosuppressive, their administrations are normally contraindicated in patients with active

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**Fig. 2.** (A) Forest plot of studies reporting hazard ratio (HR) that investigates the mortality rate between Tocilizumab (TCZ) group and standard treatment (STD) group. (B–E) Forest plot of pooled studies evaluating mortality rate, invasive mechanical ventilation (IMV) requirement, ICU admissions, and the number of discharged patients between Tocilizumab (TCZ) group and standard treatment (STD) group, respectively.
### Table 3
The characteristics of included studies on IL-6 gene polymorphism and pneumonia.

| First author, Year | Age group | Country         | Ethnicity  | Sample size (cases/controls) | Genotype (wt/wt/mtm/mtm) | p value for HWE | NOS score |
|-------------------|-----------|-----------------|------------|-------------------------------|--------------------------|----------------|-----------|
| Endeman, 2011     | Adult     | The Netherlands | Caucasian  | 200/311                       | 83/92/25                 | 0.878          | 8         |
| Mao, 2016         | Adult     | China           | Asian      | 162/200                       | 68/46/48                 | 0.000          | 8         |
| Martinez-Ocana, 2013 | Adult      | Mexico          | Caucasian  | 65/46                         | 53/12/0                  | 0.576          | 8         |
| Martin-Leeches, 2012 | Adult      | Spain           | Caucasian  | 953/1246                      | 581/516/130              | 0.752          | 8         |
| Salnikova, 2013 [a] | Adult     | Russia          | Caucasian  | 334/141                       | 37/80/22                 | 0.299          | 8         |
| Salnikova, 2013 [b] | Adult     | Russia          | Caucasian  | 216/105                       | 32/56/12                 | 0.009          | 8         |
| Schaaf, 2005      | Adult     | Germany         | Caucasian  | 100/50                        | 29/51/20                 | 0.812          | 8         |
| Sole-Violan, 2010 | Adult     | Spain           | Caucasian  | 1413/1622                     | 533/485/120              | 0.288          | 8         |
| Zhao, 2017        | Pediatric | China           | Asian      | 415/300                       | 39/24/0                  | 0.907          | 8         |
| Zidan, 2014       | Pediatric | Egypt           | African    | 100/111                       | 32/55/13                 | 0.323          | 8         |
| Chou, 2016        | Adult     | Taiwan          | Asian      | 279/156                       | 184/62/33                | 0.000          | 8         |
| Su, 2019          | Pediatric | China           | Asian      | 438/423                       | 206/193/39               | 0.000          | 8         |

### Table 4
Meta-analysis results of IL-6 gene polymorphism and pneumonia.

| Genetic model | Group          | No. of studies | Test of association | Test of heterogeneity | p Egger's test |
|---------------|----------------|----------------|---------------------|-----------------------|----------------|
| A. Case - Control |                |                |                     |                       |                |
| – 174G/C [rs1800795] |                |                |                     |                       |                |
| C vs. G       | Overall        | 10             | 1.02 (0.88; 1.18)   | 0.776 Random          | 0.006 60.71   | 0.477 |                |
|               | Overall*       | 8              | 1.02 (0.94; 1.10)   | 0.591 Fixed           | 0.260 21.23   | 0.502 |                |
| C vs. CC+GC    | Overall        | 8              | 0.92 (0.69; 1.18)   | 0.462 Random          | 0.015 59.41   | 0.443 |                |
|               | Overall*       | 7              | 0.97 (0.75; 1.24)   | 0.833 Random          | 0.051 51.99   | 0.694 |                |
| C vs. GG       | Overall        | 8              | 1.04 (0.94; 1.15)   | 0.432 Fixed           | 0.040 3.64    | 0.211 |                |
| C vs. GG       | Overall*       | 8              | 0.94 (0.72; 1.24)   | 0.690 Random          | 0.033 53.86   | 0.514 |                |
| C vs. GG       | Overall        | 10             | 1.10 (0.91; 1.33)   | 0.312 Random          | 0.028 51.82   | 0.229 |                |
| C vs. GG       | Overall*       | 8              | 1.04 (0.93; 1.16)   | 0.447 Fixed           | 0.243 23.34   | 0.252 |                |
| – 572G/C [rs1800797] |                |                |                     |                       |                |
| G vs. G        | Overall        | 2              | 2.06 (0.57; 7.45)   | 0.268 Random          | 0.000 97.25   | NA    |                |
| GG vs. CC+GG   | Overall        | 2              | 1.70 (0.62; 4.65)   | 0.293 Random          | 0.002 80.90   | NA    |                |
| GG vs. CC vs. CC | Overall      | 2              | 2.46 (0.50; 11.97)  | 0.262 Random          | 0.000 97.26   | NA    |                |
| GG vs. CC      | Overall        | 2              | 2.23 (0.51; 9.75)   | 0.284 Random          | 0.000 90.90   | NA    |                |
| GG vs. CC      | Overall        | 2              | 2.54 (0.51; 12.49)  | 0.251 Random          | 0.000 96.50   | NA    |                |
| C vs. G        | Overall        | 5              | 1.33 (1.04; 1.69)   | 0.019 Random          | 0.015 67.44   | 0.320 |                |
| C vs. G        | Caucasian      | 4              | 1.15 (1.00; 1.33)   | 0.049 Fixed           | 0.040 0       | 0.043 |                |
| C vs. G        | Overall        | 5              | 1.42 (0.98; 2.06)   | 0.058 Random          | 0.088 50.60   | 0.743 |                |
| C vs. G        | Caucasian      | 4              | 1.16 (0.85; 1.57)   | 0.331 Fixed           | 0.842 0       | 0.002 |                |
| C vs. G        | Overall        | 5              | 1.20 (1.07; 1.53)   | 0.006 Fixed           | 0.240 27.16   | 0.059 |                |
| C vs. G        | Caucasian      | 4              | 1.21 (0.99; 1.47)   | 0.054 Fixed           | 0.308 16.64   | 0.061 |                |
| C vs. G        | Overall        | 5              | 1.55 (1.18; 2.03)   | 0.001 Fixed           | 0.121 45.15   | 0.561 |                |
| C vs. G        | Caucasian      | 4              | 1.28 (0.92; 1.77)   | 0.131 Fixed           | 0.391 0       | 0.004 |                |
| C vs. G        | Overall        | 5              | 1.17 (0.96; 1.43)   | 0.103 Fixed           | 0.460 0       | 0.229 |                |
| C vs. G        | Caucasian      | 4              | 1.20 (0.98; 1.48)   | 0.076 Fixed           | 0.371 4.21    | 0.086 |                |

Bold values indicate statistically significant differences between severe and non-severe cases. Asterisk (*) indicates that studies deviated from HWE (Hardy–Weinberg equilibrium) were excluded.

Infection, thrombocytopenia, and an elevated liver function, which is also observed in COVID-19-infected patients\(^2\) (Supp. Ref. 11). Interestingly, however, pooled results collected from nine studies indicated that anti-IL-6R antibody treatment could effectively treat severe COVID-19-infected patients, marked by suppression of CRP and improvement of clinical symptoms. This may be due to transcriptional induction of the CRP gene was inhibited by TCZ, which then further suppressed inflammatory responses during SARS-
CoV-2 infection. Although IL-6 gene polymorphism results may not directly correlate with novel coronavirus pneumonia (NCP), this analysis demonstrated that IL-6 −174C allele carrier status is associated with higher level of IL-6 production and more severe forms of pneumonia in general. This analysis strengthens the notion that IL-6 plays a pivotal role in novel coronavirus pneumonia (NCP) progression.

At present, 32 clinical trials have been registered (clinicaltrials.gov) to evaluate the efficacy and safety of anti-IL-6R antibodies. Despite the limited number of participants so far, suppression of IL-6 signaling cascade shows a promising therapy in the ARDS induced by SARS-CoV-2 infection.

**Conflict of interest**

None to declare.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2020.07.002.

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