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References

1 Barton SH, Murray JA. Celiac disease and autoimmunity in the gut and elsewhere. Gastroenterol Clin North Am 2008;37:411–28.

2 Mirza N, Bonilla E, Phillips PE. Celiac disease in a patient with systemic lupus erythematosus: a case report and review of literature. Clin Rheumatol 2007;26:827–8.

3 Lerner A, Blank M, Lahat N *et al*. Increased prevalence of autoantibodies in celiac disease. Dig Dis Sci 1998;43:723–6.

4 Lawlor DA. Commentary: two-sample Mendelian randomization: opportunities and challenges. Int J Epidemiol 2016;45:908–15.

5 Trynka KA, Hunt NA, Bockett *et al*. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet 2011;43:1193–201.

6 Hom G, Graham RR, Modrek B *et al*. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. New Engl J Med 2008;358:900–9.

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No higher risk of respiratory symptoms in Italian rheumatological patients under IL-6R-inhibitor therapy in SARS-CoV-2 pandemic

Rheumatology key message

- Concomitant IL-6R-inhibitor doesn't increase respiratory symptoms rate in Italian rheumatological patients during the SARS-CoV-2 pandemic.

Dear Editor, In these days of severe acute respiratory syndrome virus (SARS-CoV-2) infection outbreak all over the world, an initial report describing the clinical course of rheumatological patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) in a high incidence area of SARS-CoV-2 infection in Italy, Lombardy, became available [1].

In routine clinical care, there are many questions and special anxieties for people with rheumatic diseases who are taking immunosuppressive medicines like steroids, biological or conventional-DMARDs such as methotrexate. Because immunosuppressive drugs are useful to prevent a worsening of concomitant rheumatological conditions, if stopped, patients may experience a disease flare. However, despite the fact that the effect of these drugs on increasing the risk of SARS-CoV-2 infection is not fully known, the rheumatological scientific community advises not to stop or reduce medications unless suggested by clinicians due to specific reasons [2].

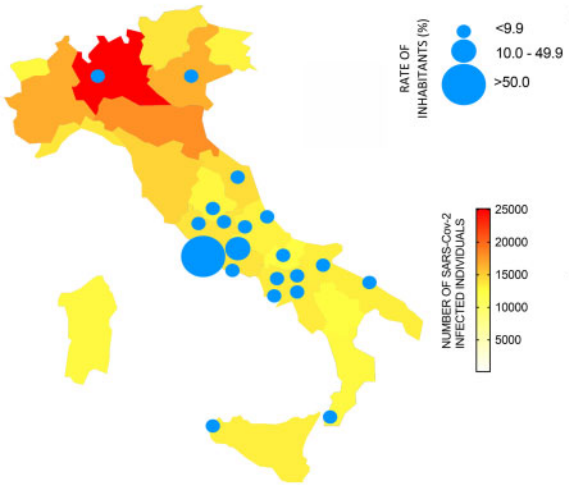
It has been reported that severe and critical complications of SARS-CoV-2 infection lead to multiorgan failure due to aberrant host response towards infection characterized by the release of pro-inflammatory cytokines (IL-6 and TNFα) whose levels are associated with the disease severity with a decline back to normality in the recovery phase [3]. Based on these assumptions, anti-IL-6R inhibition was approved for the treatment of cytokines storm syndrome [4], and then included in multiple countries within SARS-CoV-2-induced treatment flow-charts.

Based on this, to address the issue on how to deal with patients with chronic treatment with b-DMARDs in the setting of SARS-CoV-2 infection and on how concomitant c-DMARDs may affect the epidemiology of respiratory symptoms in rheumatological patients, we enrolled in a prospective survey 146 patients under treatment with IL-6R-inhibitor (tocilizumab or sarilumab) [IL-6R-i duration: 32.9 (2.5) months] [133 (91.1%) for rheumatoid arthritis, 10 (6.8%) for giant cell arteritis and 3 (2.1%) for systemic sclerosis, respectively] in the Division of Rheumatology at Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome. Each enrolled patient was interviewed about the incidence of fever and respiratory symptoms such as cough, sore throat and dyspnoea in the last 12 weeks (1 January to 3 March 2020). All patients had provided their informed consent for the use of personal and clinical data for scientific purposes, and no patient refused to participate. As shown in Fig. 1A, the majority of our patients were living in central-southern Italian regions, whose demographic and clinical characteristic are summarized in Fig. 1B. Among the whole cohort, patients reported only mild respiratory symptoms and no-one declared previous contact with confirmed SARS-CoV-2^{pos} individuals. Moreover, early clinical results showed that antimalarial drugs may have effective *in vitro* anti-viral properties against SARS-CoV-2 [5], stratifying the whole cohort based on the concomitant use of antimalarials + IL-6R-inhibitor we found no significant differences in terms of incidence of fever and respiratory symptoms comparing treated and untreated patients. Moreover, considering the concomitant use of other c-DMARDs (methotrexate, sulphasalazyne and leflunomide, alone or in combination) + IL-6R-inhibitor, there was no increased risk of occurrence of fever and respiratory symptoms compared with patients under IL-6R-inhibitor monotherapy. However, considering the concomitant use of steroids [daily dose: 4.8 (0.5) mg], patients under IL-6R inhibitor and cDMARDs + concomitant steroid therapy, showed higher rate of fever (17.9%) and sore throat (20.5%) compared with patients under IL-6R-inhibitor monotherapy in the previous 12 weeks (0.0% had fever, P =0.017; and 3.5% had sore throat, P =0.041) (Fig. 1C).

Despite being unable to stratify patients based on IL-6R-inhibitor indication, our data support the current policy of the rheumatological community to suggest not to stop conventional or biologic-DMARDs therapies where otherwise indicated, despite the fact that low-dose steroid seems to be avoided if possible. This finding is in line with the recently published case series describing the

FIG. 1 Impact of SARS-Cov-2 pandemic on rheumatologic patients under IL-6R-inhibitor in central-south Italy

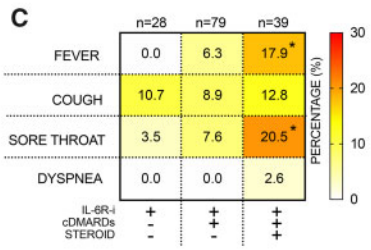
A



B

VARIABLES	Whole cohort of patients under IL-6R-inibitor therapy (n=146)			p	p^a	p^b
	Monotherapy (n=28)	Combination with cDMARDs (n=79)	Combination with cDMARDs + steroid (n=39)			
Female, n(%)	24 (85.7)	65 (82.3)	33 (84.6)	*0.676*	*0.901*	*0.750*
Age, years (mean ± s.e.m.)	58.0 ± 2.5	53.8 ± 1.7	54.4 ± 2.0	*0.154*	*0.145*	*0.817*
IL-6R-i duration, months (mean ± s.e.m.)	33.5 ± 5.5	34.9 ± 3.2	34.9 ± 5.4	*0.905*	*0.844*	*0.740*
Anti-pneumococcal vaccine, n(%)	4(14.3)	8 (10.1)	7 (17.9)	*0.549*	*0.689*	*0.230*
Anti-influenza vaccine, n(%)	11(39.3)	23 (29.1)	17 (43.6)	*0.321*	*0.724*	*0.118*
Arterial Hypertension, n(%)	6 (21.4)	19 (24.1)	14 (35.9)	*0.778*	*0.202*	*0.177*
Antimalarials usage, n(%)	-	24 (30.4)	12 (30.8)	-	-	*0.965*
Methotrexate usage, n(%)	-	55 (69.6)	21 (53.8)	-	-	*0.092*
Methotrexate dose, mg/week (mean ± s.e.m.)	-	12.6 ±0.5	14.4 ± 0.9	-	-	*0.121*
Sulphasalazyne usage, n(%)	-	7 (8.9)	5 (12.8)	-	-	*0.503*
Leflunomide usage, n(%)	-	11 (13.9)	10 (25.6)	-	-	*0.117*
Concomitant cDMARDs, (mean ± s.e.m.)	-	1.2 ± 0.0	1.2 ± 0.1	-	-	*0.907*
Steroid usage, n(%)	-	-	39 (100.0)	-	-	-
Prednisone dosage, mg/day (mean ± s.e.m.)	-	-	4.8 ± 0.5	-	-	-

C



A) Distribution of the study cohort in relation to the number of SARS-Cov-2 infected people in Italy. The different regions have been coloured based on the registered cases of SARS-Cov-2pos individuals by the Ministry of Health on 31 March 2020 (www.salute.gov.it). The size of the blue dots relates to the percentage of study participants coming from the reference city/town. **B**) Demographic, clinical and therapeutic characteristics of the study cohort. **C**) Rate of fever and respiratory symptoms in rheumatological patients under IL-6R-inhibitor treatment alone or in combination with cDMARDs and/or steroid; *P <0.05 patients under IL-6R-inhibitor monotherapy *vs* patients under c-DMARDs + IL-6R-inhibitor + steroid combination therapy. cDMARDs: conventional disease modifying anti-rheumatic drugs; SARS: severe acute respiratory syndrome; S.E.M.: standard error of the mean; IL-6R: interleukin-6 receptor. *P*: IL-6R-inhibitor monotherapy *vs* IL-6R-inhibitor + cDMARDs; pa: IL-6R-inhibitor monotherapy *vs* IL-6R-inhibitor + cDMARDs + steroids; pb: IL-6R-inhibitor + cDMARDs *vs* IL-6R-inhibitor + cDMARDs + steroids.

clinical course of patients with immune-mediated diseases with SARS-CoV-2 infection in the New York area, in whom the concomitant use of oral glucocorticoids, hydroxychloroquine and methotrexate was higher among patients for whom hospitalization was warranted [6]. Therefore, a better understanding of the implications of SARS-CoV-2 infection in patients with immune-mediated inflammatory diseases and the effects of conventional and biologic-DMARDs is urgently needed to guide clinicians in patient care. In this contest, ongoing initiatives promoted by National Rheumatological Societies [7], EULAR and the American College of Rheumatology are working on an integrated repository of global information about SARS-CoV-2 infection, which will provide useful information on the risk of infection in rheumatological patients and on its relation with immunosuppressive treatments.

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References

1 Monti S, Balduzzi S, Delvino P *et al*. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020;79:667–8.

2 News SIR The Italian Society of Rheumatology answers to patients about COVID-19 pandemic. https://www.reumatologia.it/cmsx.asp?IDPg=1087 (25 June 2020, date last accessed).

3 Chen G, Wu D, Guo W *et al*. Clinical and immunologic features of severe and moderate Coronavirus Disease 2019. J Clin Invest 2020;130:2620–9.

4 Chen H, Wang F, Zhang P *et al*. Management of cytokine release syndrome related to CAR-T cell therapy. Front Med 2019;13:610–7.

5 Wang M, Cao R, Zhang L *et al*. Cell Res 2020;30:269–71.

6 Haberman R, Axelrad J, Chen A *et al*. Covid-19 in immune-mediated inflammatory diseases - case series from New York. N Engl J Med 2020; advance access published 29 April 2020, doi: 10.1056/NEJMc2009567.

7 News SIR The Italian Society of Rheumatology Registry of COVID-19 infected patients. https://www.reumatologia.it/cmsx.asp?IDPg=1092 (25 June 2020, date last accessed).