

The differential response to anti IL-6 treatment in COVID-19: the genetic counterpart

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The outbreak of the SARS-CoV-2 infection has posed the world at a pandemic risk. The disease (COVID-19) is characterised by an acute respiratory distress and anti-IL6 therapy with tocilizumab has been used as a potential treatment (1). This drug has demonstrated to be a good therapeutic option for rheumatoid arthritis (RA) but its clinical experience in viral diseases is extremely limited (2). Moreover, high costs and safety risks may be a barrier for its wide use in COVID-19 and lack of response can be seen in up to 20% of RA patients. The identification of genetic markers as predictors of response can help for selecting responders to tocilizumab during COVID-19 pandemic. So far, several single-nucleotide polymorphisms (SNPs) have been identified to predict response to tocilizumab. Strongest associations were found with *CD69* (rs11052877), *GALNT18* (rs4910008), *CLEC2D* (rs1560011), *KCNMB1* (rs703505), *ENOX1* (rs9594987) genes and rs10108210, rs703297 variants (3). *GALNT18* and *CD69* were confirmed associated with EULAR response, low disease activity (LDA) and DAS28 improvement (4). Another gene influencing tocilizumab response seems to be the *FCGR3A* (5). Concerning the *IL-6R* gene, results suggest that carriers of rs12083537 AA genotype and CC for rs11265618 have a better response to treatment (6, 7) although this was not confirmed in other studies (8).

In a very preliminary analysis, we tested the contribution of two coding polymorphisms and an intronic polymorphism, respectively rs33980500, rs13190932 and rs13196377 of *TRAF3IP2* gene, as genetic markers of response to tocilizumab in RA patients. *TRAF3IP2* codes for Act1, a signalling adaptor that works as a positive signalling adaptor in IL-17-mediated cellular immune responses, while concomitantly is a negative regulator of adaptive immunity by inhibiting CD40- and BAFFR-mediated signalling (9). We have already reported that *TRAF3IP2* variant allele rs33980500 was associated with lack of LDA and remission achievement at 6 months in RA patients treated with anti-TNF (adalimumab and etanercept) and no EULAR response at 2 years in etanercept treated patients (10). Herein, 21 patients (F:19, M:2) suffering from moderate to severe RA according to 2010 EULAR/ACR classification criteria, treated with monthly intravenous tocilizumab 8 mg/kg were evaluated (baseline - mean age 65.4±11.5 years old, mean disease duration 14.3±8.4 years; erythrocyte sedimentation rate 57.6±28.7 mm/h; C-reactive protein 12.2±20.2 mg/dl, DAS28 6.7±1.1). All of the patients gave their written informed

Table I. Association between *TRAF3IP2* rs33980500 and EULAR response at 12 months.

<i>TRAF3IP2</i> _rs33980500		No EULAR response (n=12)	Good/Moderate EULAR response (n=9)	p
Genotypes	CC	41.7%	88.9%	0.041*
	CT	50%	0	
	TT	8.3%	11.1%	
Genotypes	CC	41.7%	88.9%	0.067
	CT+TT	58.3%	11.1%	

consent. DNA was extracted using a Qiagen blood DNA mini Kit. Genotyping of the three SNPs was performed by allelic discrimination assay by TaqMan technology using MGB-specific allelic probes (coded C__2473124_10, C__2473123_20 and C__2475647_10 respectively) and ABI PRISM 7500. In this preliminary study we found that rs33980500 polymorphism of *TRAF3IP2* appears to show a promising association with good or moderate EULAR response at 12 months ($p=0.041$; noticeably the statistical significance appears borderline probably due to the small cohort, Table I), suggesting that also IL-17 pathway may be influenced in the course of tocilizumab treatment.

Thus, several genes but especially polymorphisms in *GALNT18*, *CD69* and *IL6R* genes are promising biomarkers of response to tocilizumab in RA. It is not known if these are the same genetic markers that could prove useful in the context of COVID-19. Genetic tests can be time consuming thus there may be the need to develop feasible kits. Identification of markers of response to tocilizumab in SARS-CoV-2 can allow a personalised targeted therapy and can spare the usage of immunosuppressants to treat a viral disease. Also, genetic biomarkers may predict not only response to therapy but also development of adverse events. In turn, this can represent an economic saving, especially in the woeful arise of the pandemic in poorer countries. Finally, depicting the genetic background of pharmacogenetics in COVID-19 will allow a better comprehension of the disease pathogenic mechanisms.

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