Pharmacogenetic determinants of response to infliximab in pediatric inflammatory bowel disease

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Anti-tumor necrosis factor (TNF) agents, in particular infliximab, have become the mainstay of treatment in refractory inflammatory bowel diseases (IBD), also in pediatric patients. Furthermore, they also seem to be promising as first line treatment in the early stages of disease, yet their widespread use may not be affordable by the National Health Service. While the general mechanism of action of anti-TNF agents has been investigated, it is still largely unknown why clinical response differs among patients. Currently, there are no clinical, pharmacological or molecular predictors of response to anti-TNF therapy available for translation in clinical practice. In fact, interindividual differences in response to therapy could be influenced by several interacting factors. Therefore, strategies integrating clinical, pharmacokinetic, pharmacodynamic and pharmacogenomic information could lead to the identification of subsets of patients with a higher probability of response and to personalization of anti-TNF treatment, resulting in more cost-effective therapies. Loss of response in patients treated with infliximab may be in part the result of failure to achieve and maintain adequate drug levels and/or of the formation anti-infliximab antibodies. Recent findings also suggest that membrane TNF expression on the intestinal mucosa may predict therapeutic response (1). Several studies have evaluated the effect of genetic variants in candidate genes involved in infliximab pharmacokinetics and pharmacodynamics on the response to the medication even if no unique marker has been identified; recent studies however indicate that relevant variants to predict infliximab response are those in *IL6* and *TNF* genes (2). The aim of the present study was therefore to evaluate the role of these candidate genetic factors on the response to infliximab in an Italian cohort of children and young adults with IBD. Patients with IBD treated with infliximab were enrolled by the Department of Pediatrics of Burlo Garofolo Children's Hospital in Trieste; clinical data were collected retrospectively. Response to infliximab was evaluated as a decrease in disease activity score after induction therapy and as the need to switch therapy with infliximab within 12 months of follow-up. The most relevant functional SNP for each gene considered were characterized by PCR-RFLP (rs1800795, -174G/C in *IL6* and rs1800629, -308A/G in *TNF*) assays on patients' DNA extracted from peripheral blood. Sixty-four young patients with IBD were enrolled. Of these, 48.4% were female, median age at infliximab start was 13.4 years (interquartile range, IQR 10.9–16.1). IBD diagnosis was Crohn's disease in 65.6% and ulcerative colitis in 34.4%. At the beginning of infliximab therapy, disease had been lasting for a median of 1.1 year (IQR 0.53–2.5); infliximab was administered at a dose of 5 mg/kg according to the standard schedule. Genotyping showed minor allele frequencies of 39.8% for rs1800795, 10.1% for rs1800629, consistent with previous reports in Europeans. Assessment of response to infliximab showed that 21.9% of patients did not respond to induction therapy; moreover, 36.8% needed to switch therapy within 12 months. Genotyping analysis identified an association between the homozygous CC variant of *IL6* and diminished response to induction therapy: frequency of non-response in patients with this genotype was almost three times that of patients with a GG/GC genotype ($p<0.05$). This is the first study evaluating the effect of pharmacogenetic variants on response to infliximab in Italian patients with pediatric IBD, showing relevant associations. This report supports the utility of genotyping candidate genes to predict infliximab response in children with IBD and should be further validated by larger and prospective studies and improved by integrating pharmacokinetic and pharmacodynamic evaluations.

1. Atreya R et al. Nat Med 2014
2. Fabris M et al. Pharmagogenomic J 2015