Multi-alleles predict primary non-response to infliximab therapy in Crohn’s disease

Cai-Bin Zhang1,†, Jian Tang2,3,†, Xue-Ding Wang1, Kun-Sheng Lyu4, Min Huang1,* and Xiang Gao2,3,*

1Institute of Clinical Pharmacology, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, Guangdong, P. R. China; 2Department of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P. R. China; 3Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P. R. China; 4Southern China Center for Statistical Science School of Mathematics, Sun Yat-sen University, Guangzhou, Guangdong, P. R. China

*Corresponding author. Min Huang, School of Pharmaceutical Sciences, Sun Yat-sen University, 132 East Circle at University City, Guangzhou 510006, P. R. China. Tel: +86-20-39943027; Fax: +86-20-87335429; Email: huangmin@mail.sysu.edu.cn; Xiang Gao, Department of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, No. 26 Yuancun Road II, Tian He District, Guangzhou, Guangdong 510000, P. R. China. Tel: +86-13502405878; Fax: +86-20-38254101; Email: helengao818@163.com
†These authors contributed equally to this work.

Abstract

Background: Infliximab (IFX) is the first-line treatment for patients with Crohn’s disease (CD) and is noted for its relatively high cost. The therapeutic efficacy of IFX has noticeable individual differences. Known single-gene polymorphisms (SNPs) are inadequate for predicting non-response to IFX. In this study, we aimed to identify new genetic factors associated with IFX-therapy failure and to predict non-response to IFX by developing a multivariate predictive model.

Methods: In this retrospective study, we collected and analysed the data of Chinese patients with CD who received IFX therapy at one hospital between June 2013 and June 2019. Primary non-response (PNR) and non-durable response (NDR) were evaluated using a simple endoscopic score for CD (SES-CD). A total of 125 SNPs within 44 genes were genotyped. A multivariate logistic-regression model was established to predict non-response to IFX. An area-under-the-receiver-operating-characteristics curve (AUROC) was applied to evaluate the predictive model performance.

Results: Forty-two of 206 (20.4%) patients experienced PNR and 15 of 159 (9.4%) patients experienced NDR. Nine SNPs were associated with PNR (P < 0.05). A PNR predictive model was established, incorporating 2-week high-sensitivity C-reactive protein (hs-CRP), rs61886887, rs61740234, rs357291, rs2269330, and rs111504845, and the AUROC on training and testing data sets were 0.818 (P < 0.001) and 0.888 (P < 0.001), respectively. At week 14, hs-CRP levels ≥ 2.25 mg/L were significantly associated with NDR (AUROC = 0.815, P < 0.001). PNR-associated SNPs were not mutually associated with NDR, suggesting distinct mechanisms between PNR and NDR.

Conclusion: Genetic polymorphisms are significantly associated with response to IFX among Chinese CD patients.
Key words: infliximab; Crohn’s disease; single nucleotide polymorphism; therapeutic response

Introduction

Crohn’s disease (CD) is a complex chronic inflammatory disease of the gastrointestinal tract that can induce progressive bowel damage and disability [1]. Infliximab (IFX), a chimeric monoclonal antibody, is now firmly established as an effective therapeutic approach for inflammatory bowel disease (IBD) despite its high cost [2]. However, 15%–40% of IBD patients experience primary IFX-treatment failure [3, 4] and secondary loss of response is estimated to occur at a rate of 13% per year [5]. The high cost of treatment and the high rate of resistance to therapy make it imperative to identify patients who are likely to fail IFX therapy as soon as possible and change their treatment to a more cost-effective alternative.

Despite large inter-individual differences in the therapeutic efficacy of IFX, few practical and accurate indicators are available to predict IFX therapeutic efficacy. Many clinical and genetic factors have been observed to affect the therapeutic efficacy of IFX [6–11]. However, only one study, by Barber et al. [12], has integrated clinical characteristics and genetic factors, and treated subjects with multiple monoclonal antibodies, including adalimumab and infliximab. A recent study by Quistrebert et al. [13] showed that the cumulative incidence of anti-drug antibody (ADA) varied significantly between patients treated with adalimumab and infliximab. However, the ADA level influences the clinical outcomes of monoclonal-antibodies therapy [14–16]. Therefore, the predictors provided in the study by Barber et al. [12], which are based on heterozygous patients (treated with different antibodies), may not be accurate enough for patients treated with IFX alone.

In this study, we comprehensively analysed the clinical characteristics and genetic factors of CD patients who received IFX alone, aiming to explore the practical genetic biomarkers that can indicate IFX therapeutic efficacy and identify patients non-responsive to IFX therapy. Also, by establishing a multigenetic predictive model and individualizing IFX therapy, we aimed to potentially reduce patients’ healthcare costs.

Patients and methods

Patients and data collection

This retrospective study included Chinese patients with CD who were scheduled for IFX induction therapy at the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between 1 June 2013 and 1 June 2019. All patients were treated with 5 mg/kg of IFX at weeks 0, 2, and 6 during induction therapy, and 5 or 10 mg/kg of IFX every 8 weeks during maintenance therapy. We collected and analysed patients’ demographic and clinical data, including sex, age, body mass index (BMI), disease duration, disease behavior and location, perianal lesions, previous bowel surgery, co-administration with thiopurine immunosuppressive therapy, and laboratory values including serum albumin and high-sensitivity C-reactive protein (hs-CRP) levels. The study protocol was approved by the ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China (IRB approval number: 2018ZSLYEC-091). All patients provided signed informed consent.

Concentrations of infliximab and ADAs

We collected serum samples at week 14 to detect the concentrations of IFX and ADAs. Concentrations of IFX and ADAs were measured by using an enzyme-linked immunosorbent assay (Immundiagnostik AG, Germany) according to the manufacturer’s instructions.

Genotyping

Patients’ DNA was extracted from ethylene diamine tetraacetic acid blood samples using the TIANamp Genomic DNA Kit (Tiangen Biotech, Beijing, China) and was stored at −80 °C until use. We analysed 125 tag SNPs within 44 genes (IBD-susceptibility genes, inflammatory-related genes, apoptosis-related genes, IgG Fc-receptor family genes). The characteristics of all tag SNPs are shown in Supplementary Table 1. Tag SNPs were genotyped using the MassArray Analyzer system (Sequenom, Inc., San Diego, CA, USA) according to the manufacturer’s instructions. The linkage disequilibrium was calculated using Haploview bioinformatics software version 4.2 (Broad Institute, Cambridge, MA, USA), as previously described [17]. The Hardy–Weinberg equilibrium and inherence model was analysed by SNPStats [18]. The best model for a specific SNP depends on the lowest Akaike’s Information Criterion value.

Definitions of therapeutic outcomes

Simple endoscopic score for Crohn’s disease (SES-CD) values were reported by endoscopists. Primary non-response (PNR) was evaluated at week 14 and non-durable response (NDR) was evaluated at weeks 22–52, which were defined as a decrease from baseline in SES-CD of <50% with simultaneous SES-CD > 2 [19].

Statistical analysis

Descriptive statistics were provided with median and interquartile range (IQR) or 95% confidence interval (CI) for continuous non-normally distributed variables, or with mean and standard deviation (mean ± SD) for normally distributed data, respectively. The Mann–Whitney U test (two groups) and the Kruskal–Wallis test (more than two groups) were applied to compare continuous non-normal variables and the unpaired t-test (two groups) was used to analyse normal variables. Fisher’s exact or Chi-square test was used to analyse discrete variables. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

In order to establish a predictive model, all patients were randomly divided into training data sets (60%) and testing (40%) data sets. This data-set-splitting process was repeated 100 times to eliminate the randomness and, therefore, we obtained 100 training data sets and 100 testing data sets. Each training data set was fitted using the least absolute shrinkage and selection operator (LASSO) [20] to perform variable selection. Then, the frequency of the variables included in the LASSO procedure were counted and added one after another into the logistic-regression model according to their frequency from high to low in 100 training data sets, until the mean area-under-the-receiver-operating-characteristic curve (AUROC) had no obvious increase. Thereafter, the split with an AUROC closest to the average for the logistic-regression model was chosen as a representative split. The multivariate model was established in representative training data sets and validated in representative testing data sets. A receiver-operating-characteristic (ROC)
curve was applied to evaluate the performance of the multivariate model, the optimal threshold predictive value of the multivariate-regression model was identified using maximum Youden’s index. Multivariate-regression-model analysis was performed using the statistical language R (version 3.4.1, Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Patients’ characteristics**

A total of 206 eligible Chinese patients with CD were included in this study. Disease and patient characteristics are depicted in Table 1. Of these patients, 42 (20.4%) experienced PNR during IFX induction therapy and 164 (79.6%) achieved primary response. Among the 164 patients who achieved primary response to IFX, 159 received colonoscopy at weeks 22–52; 15 of 159 (9.4%) patients were NDR to IFX therapy. No effects of patients’ sex, age, BMI, disease characteristics, previous bowel surgery, and co-administration with thiopurine on primary response to IFX were observed (Table 1). Patients’ serum albumin and high-sensitivity C-reactive protein (hs-CRP) levels were recorded at weeks 2 and 14, as well as IFX levels and ADAs at week 14. Compared with patients with a primary response to IFX, PNR patients had higher hs-CRP levels at week 2 (2.1 mg/L [1.0–8.2] vs 1.0 mg/L [0.4–3.0], median and interquartile range [IQR]: P < 0.001), lower albumin levels at week 14 (41.0 g/L [36.9–42.7] vs 43.6 g/L [41.1–46.6], median and IQR; P < 0.001), and greater likelihood of ADAs (odds ratio = 3.78, P = 0.001) (Table 1). A higher hs-CRP level at week 14 is an indicator of durable response to IFX therapy. Compared with hs-CRP levels in patients with a durable response to IFX, NDR patients had higher hs-CRP levels at week 14 (4.8 mg/L [2.0–12.3] vs 1.0 mg/L [0.4–2.3], median and IQR; P < 0.001). Other clinical characteristics had no associations with NDR status (P > 0.05) (Supplementary Table 2).

**Genotypes and PNR**

A total of 125 tag SNPs within 44 genes were detected. Of these, 2 SNPs had no minor allele and 12 SNPs were not in the Hardy-Weinberg equilibrium, so they were excluded from subsequent analysis, as shown in Supplementary Table 1. Chi-square-tests analysis showed that 9 of the remaining 111 tag SNPs were significantly associated with PNR (P < 0.05), as listed in Table 2. None of the other 102 SNPs was potentially associated with PNR (Supplementary Table 3).

**Multivariate predictive model for PNR**

To establish a multivariate predictive model for PNR, we used the LASSO method to select variables as listed in Table 2 and Supplementary Table 3. The frequencies of those SNPs from the LASSO procedure were counted and added one after another.

### Table 1. Relationships between patients’ characteristics and PNR

| Demographic and clinical characteristic | Primary non-responders | Primary responders | P-value* |
|----------------------------------------|------------------------|-------------------|----------|
|                                       | (n = 42)               | (n = 164)         |          |
| Sex                                    |                        |                   |          |
| Male, n (%)                            | 33 (78.6)              | 120 (73.2)        | 0.475    |
| Female, n (%)                          | 9 (21.4)               | 44 (26.8)         |          |
| Age, years, median [IQR]               | 23.5 [16.8–33.5]       | 23.0 [18.0–27.6]  | 0.312    |
| BMI, kg/m², median [IQR]               | 17.4 [16.1–19.3]       | 18.3 [16.7–19.7]  | 0.105    |
| Disease duration, month, median [IQR]  | 12.0 [6.0–42.0]        | 12.0 [6.0–36.0]   | 0.826    |
| Disease behavior, n (%)                |                        |                   |          |
| B1                                     | 30 (71.4)              | 134 (81.7)        |          |
| B2                                     | 6 (14.3)               | 13 (7.9)          |          |
| B3                                     | 5 (11.9)               | 12 (7.3)          |          |
| B2 + B3                                | 1 (2.4)                | 5 (3.0)           |          |
| Disease location, n (%)                |                        |                   | 0.611    |
| L1                                     | 2 (4.8)                | 12 (7.3)          |          |
| L2                                     | 2 (4.8)                | 5 (3.0)           |          |
| L3                                     | 33 (78.6)              | 125 (76.2)        |          |
| L1 + L4                                | 0 (0)                  | 7 (4.3)           |          |
| L2 + L4                                | 0 (0)                  | 0 (0)             |          |
| L3 + L4                                | 5 (11.9)               | 15 (9.1)          |          |
| Perianal lesions, n (%)                | 29 (69.0)              | 124 (75.6)        | 0.385    |
| Previous bowel surgery, n (%)          | 8 (19.0)               | 25 (15.2)         | 0.549    |
| Combined with thiopurine, n (%)        | 20 (47.6)              | 86 (52.4)         | 0.868    |
| hs-CRP at baseline, mg/L, median [IQR] | 11.6 [6.2–29.8]        | 11.5 [6.8–15.5]   | 0.284    |
| Albumin at week 2, g/L, median [IQR]   | 40.2 [36.5–44.0]       | 42.6 [38.8–45.2]  | 0.061    |
| hs-CRP at week 2, mg/L, median [IQR]   | 2.1 [1.0–8.2]          | 1.0 [0.4–3.0]     | <0.001   |
| Albumin at week 14, g/L, median [IQR]  | 41.0 [36.9–42.7]       | 43.6 [41.1–46.6]  | <0.001   |
| hs-CRP at week 14, mg/L, median [IQR]  | 9.6 [1.7–14.2]         | 1.2 [4.2–6.2]     | <0.001   |
| IFX level at week 14, µg/ml, median [IQR] | 1.5 [0.6–3.5]         | 3.8 [1.7–6.7]    | <0.001   |
| ADAs positive at week 14, n (%)       | 15 (35.7)              | 22 (13.4)         | 0.001    |

PNR, primary non-response; BMI, body mass index; B1, non-stricturing non-penetrating; B2, stricturing; B3, penetrating; L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal; hs-CRP, high-sensitivity C-reactive protein; IFX, infliximab; ADAs, anti-drug antibodies.

*Chi-square tests or Mann–Whitney U test.
Table 2. Genotypes and primary non-response to infliximab

| Gene          | rs number | Genotype   | Inherence model | P-valuea | OR      | 95% CI       |
|--------------|-----------|------------|-----------------|----------|---------|--------------|
| C1orf106     | rs61740234| CC+TT vs CT| Overdominant    | 0.010    | 4.49    | 1.31–15.32   |
| CCDC88B      | rs61886887| TT+TC vs CC| Dominant        | 0.002    | 0.08    | 0.01–0.61    |
| NF-kB1       | rs7674004 | GG+AA vs GA| Overdominant    | 0.039    | 0.47    | 0.23–0.97    |
| IL1RN        | rs3596201 | TT+CC vs TC| Overdominant    | 0.035    | 2.18    | 1.05–4.56    |
| IL17RA       | rs2241046 | TT+TC vs CC| Recessive       | 0.012    | 0.17    | 0.04–0.80    |
| OSMR         | rs357291  | AA+AC vs CC| Recessive       | 0.005    | 0.33    | 0.15–0.73    |
| TRIM21       | rs2269330 | GG+GA vs AA| Dominant        | 0.006    | 0.35    | 0.16–0.75    |
| RIPK1        | rs9378763 | AA+AC vs CC| Dominant        | 0.047    | 2.11    | 1.00–4.48    |
| FCGR3A       | rs111504845| GG+GA vs AA| Dominant        | 0.047    | 2.50    | 1.00–6.33    |

0.836 6 0.836 6 0.029, respectively. Most AUROCs for the training data sets were close to those for the testing data sets, with a difference in mean AUROC of 0.02. Therefore, the combined genetic-clinical model is stable and has no overfitting.

To develop the most accurate genetic-clinical predictive model for future use, multivariate logistic-regression analysis was performed using the entire data set, which allows the calculation of variables and determination of relative importance (Table 3). A score nomogram based on the entire data set was created and could be used easily and simply to calculate PNR to IFX therapy. It was developed using hs-CRP values at week 2 (rs61886887, rs61740234, rs357291, rs2269330, rs111504845) (Figure 3B).

**Stability and convenience of the combined genetic-clinical predictive model**

To evaluate the stability of the combined genetic-clinical model, all AUROCs of 100 training data sets and 100 testing data sets obtained from 100 data-set splitting were calculated, as shown in Figure 3A. For the 100 training data sets and the 100 testing data sets, the AUROCs were 0.813 ± 0.044 and 0.836 ± 0.029, respectively. Most AUROCs for the training data sets were close to those for the testing data sets, with a difference in mean AUROC of 0.02. Therefore, the combined genetic-clinical model is stable and has no overfitting.

**High-sensitivity C-reactive protein predicts NDR**

Although no SNPs were associated with NDR (Supplemental Table 4), we found that the 14-week hs-CRP level was significantly associated with NDR (Table 1). In estimating the accurate threshold level of 14-week hs-CRP to predict NDR, ROC-curve analysis was conducted on the entire data set. The optimal threshold level of 14-week hs-CRP was 2.25 mg/L. AUROC was 0.815 (95% CI: 0.721–0.909, P < 0.001), and sensitivity and specificity were 78.6% and 74.8%, respectively (Figure 4). This result indicates that the 14-week hs-CRP level is a valuable predictor of NDR.

**Discussion**

IFX is a mainstay therapy for moderate to severe IBD [21, 22], but the high incidence of PNR and NDR hinders its effective application.
clinical application. In the present study, a combined genetic–clinical model (with hs-CRP, C1orf106 rs61740234, CCDC88B rs61886887, OSMR rs357291, TRIM21 rs2269330, and FCGR3A rs111504845) for PNR had superior discriminatory power, with an AUROC in the representative training and testing data sets of 0.818 and 0.888, respectively. Furthermore, 14-week hs-CRP levels were demonstrated to be a useful predictor of NDR (AUROC = 0.815).

Potentially relevant parameters have been explored extensively in previous studies and several clinical risk factors were found to be associated with the therapeutic efficacy of IFX, including sex [6], duration of disease [7], albumin [8], and CRP levels [9, 23]. However, the results are inconsistent between studies. In particular, the effect of CRP, an important indicator for inflammation intensity, on therapeutic response was still very controversial. Morita et al. [24] showed that CRP levels at week 2 were significantly lower in the responders than those in the non-responders, but the same results were not found by Lee et al. [25] or Ferrante et al. [26]. In the present study, no differences were found in the baseline levels of hs-CRP between primary responders and primary non-responders to IFX. However, surprisingly, significant differences were observed in the levels of hs-CRP at week 2 between the two groups of the study population, indicating that the levels of hs-CRP were significant at week 2 in predicting response to IFX. As expected, the genetic–clinical predictive model incorporating 2-week hs-CRP levels predicted significant IFX response at week 14, with an AUROC of 0.818 (95% CI: 0.716–0.921, P < 0.001) compared to an AUROC of 0.794 (95% CI: 0.682–0.905, P < 0.001) in the genetic predictive model.

However, in the present study, no associations were found between SNPs and NDR (Supplementary Table 4). PNR-associated SNPs were not mutually associated with NDR, implying that the mechanisms of PNR and NDR are distinctive. A total of 31 SNPs reported to be significantly associated with response to IFX by Barber et al. [12], Burke et al. [27], Prieto-Perez et al. [10], and Linares-Pineda et al. [11] (Supplementary Table 5) were analysed in the present study. However, none of these was associated with IFX response in Chinese patients (Supplementary Tables 3 and 4), which may be explained by ethnic differences in genetic polymorphisms in response to IFX and by the use of multiple monoclonal antibodies in the included subjects rather than using only IFX.

The present study was strengthened by including a large number of patients whose primary endpoint was defined by endoscopy. Endoscopic results are reproducible and correlate reliably with clinical activity. Many previous studies defined therapeutic outcomes based on the CD activity index or the
Harvey–Bradshaw index. However, it must be noted that some of these indices are open to subjective interpretation [28]. In contrast, SES-CD has good reproducibility and low subjectivity [19], which help to assure the accuracy of the end points.

Nevertheless, this study has several limitations. Although nine SNPs were found to be significantly associated with PNR to IFX, additional mechanistic and clinical investigations are warranted to verify the relationships. In addition, although we tested the performance of our predictive model in a representative testing data set, a prospective study is still needed to validate the discriminatory power of this model.

In summary, in the present retrospective study, which includes a large number of CD patients, nine SNPs were identified as potential indicators of PNR to IFX, providing a basis for further exploration of underlying response mechanisms. We also developed a combined genetic–clinical model with good discriminatory power and high performance to predict PNR. Results of the present study indicate that the 14-week hs-CRP level is a competent predictor of NDR. Findings of this study may help to identify patients who are PNR and NDR to IFX therapy and may potentially reduce patients’ healthcare costs via personalized IFX therapy.

Supplementary data

Supplementary data is available at Gastroenterology Report online.
Table 3. Multivariate logistic-regression analysis in entire data set

| Variable          | β   | P-value | OR      | 95% CI       |
|-------------------|-----|---------|---------|--------------|
| hs-CRP at week 2  | 0.095 | 0.010  | 1.10   | 1.02–1.18   |
| rs61740234        | 1.130 | 0.054  | 3.10   | 0.98–9.80   |
| rs61886887        | −2.685 | 0.012  | 0.07   | 0.01–0.55   |
| rs357291          | −1.269 | 0.011  | 0.28   | 0.11–0.75   |
| rs2269330         | −1.180 | 0.009  | 0.31   | 0.13–0.74   |
| rs111504845       | 1.226 | 0.023  | 3.41   | 1.19–9.77   |

Factors were statistically analysed by multivariate logistic-regression analysis; constant is 0.839.

hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval.

Figure 4. ROC curves of the association of 14-week high-sensitivity C-reactive protein (hs-CRP) level with non-durable response (NDR) to IFX. The optimal threshold level of 14-week hs-CRP was 2.25 mg/L and the AUROC was 0.815 (95% CI: 0.721–0.909, P < 0.001). Sensitivity and specificity were 78.6% and 74.8%, respectively.

Authors’ contributions

C.B.Z. and J.T. contributed to the study design, research performance, sample collection, acquisition of data, and manuscript writing; X.D.W. contributed to the study design, data analysis, and revision of the draft; K.S.L. contributed to the study design, data analysis, and revision of the draft; M.H. and X.G., as the co-corresponding authors, were involved in the study design and revision of the draft. All authors read and approved the final version of this paper.

Funding

This study was supported by the National Natural Science Foundation of China [Grant No. 81573507, 81473283, 81173131, and 81320108027], the Natural Major Projects for science and technology development from Science and Technology Ministry of China [Grant No. 2012ZX09506001-004], the Major Scientific and Technological Project of Guangdong Province [Grant No. 2011A080300001], and the Medical Scientific Research Foundation of Guangdong Province of China [Grant No. A2020123].

Acknowledgements

None declared.

Conflicts of interest

None declared.

References

1. Baumgart DC, Sandborn WJ. Crohn’s disease. Lancet 2012;380: 1590–605.
2. Mitrev N, Vande Casteele N, Seow CH et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther 2017; 46:1037–53.
3. Buhl S, Steenholdt C, Rasmussen M et al. Outcomes after primary infliximab treatment failure in inflammatory bowel disease. Inflamm Bowel Dis 2017;23:1210–7.
4. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev 2014;13:24–30.
5. Ben-Horin S, Chowerya Y. Review article: loss of response to anti-TNF treatments in Crohn’s disease. Aliment Pharmacol Ther 2011;33:987–95.
6. Papamichael K, Rakowsky S, Rivera C et al. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn’s disease. Inflamm Bowel Dis 2018;24: 2266–71.
7. Roblin X, Boschetti G, Duru G et al. Distinct thresholds of infliximab trough level are associated with different therapeutic outcomes in patients with inflammatory bowel disease: a prospective observational study. Inflamm Bowel Dis 2017;23:2048–53.
8. Suzuki Y, Matsui T, Ito H et al. Circulating interleukin 6 and albumin, and infliximab levels are good predictors of recovering efficacy after dose escalation infliximab therapy in patients with loss of response to treatment for Crohn’s disease: a prospective clinical trial. Inflamm Bowel Dis 2015;21: 2114–22.
9. Wong U, Cross RK. Primary and secondary nonresponse to infliximab: mechanisms and countermeasures. Expert Opin Drug Metab Toxicol 2017;13:1039–46.
10. Prieto-Perez R, Almoguera B, Cabaleiro T et al. Association between genetic polymorphisms and response to anti-TNFs in patients with inflammatory bowel disease. Int J Mol Sci 2016; 17:225.
11. Linares-Pineda TM, Canadas-Garre M, Sanchez-Pozo A et al. Pharmacogenetic biomarkers of response in Crohn’s disease. Pharmacogenomics J 2018;18:1–13.
12. Barber GE, Yajnik V, Khalili H et al. Genetic markers predict primary non-response and durable response to anti-TNF biologic therapies in Crohn’s disease. Am J Gastroenterol 2016; 111:1816–22.
13. Quistrebert J, Hassler S, Bachelet D et al. Incidence and risk factors for adalimumab and infliximab anti-drug antibodies in rheumatoid arthritis: a European retrospective multicohort analysis. Semin Arthritis Rheum 2019;48:967–75.
14. Kennedy NA, Heap GA, Green HD et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn’s disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341–53.
15. Hambardzumyan K, Hermanrud C, Marits P et al. Association of female sex and positive rheumatoid factor with low serum infliximab and anti-drug antibodies, related to treatment failure in early rheumatoid arthritis: results from the SWEFOT trial population. Scand J Rheumatol 2019;48:362–6.
16. Vermeire S, Gils A, Accossato P et al. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018;11:1756283X1775035.
17. Gabriel SB, Schaffner SF, Nguyen H et al. The structure of haplotype blocks in the human genome. Science 2002;296:2225–9.
18. Sole X, Guino E, Valls J et al. SNPStats: a web tool for the analysis of association studies. Bioinformatics 2006;22:1928–9.
19. Vuitton L, Marteau P, Sandborn WJ et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65:1447–55.
20. Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Series B Stat Methodol 1996;58:267–88.
21. Brandse JF, Mathot RA, van der Kleij D et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:251–8.e2.
22. Miligkos M, Papamichael K, Vande Casteele N et al. Efficacy and safety profile of anti-tumor necrosis factor-α versus anti-integrin agents for the treatment of Crohn’s disease: a network meta-analysis of indirect comparisons. Clin Ther 2016;38:1342–58.e6.
23. Tang J, Zhang C-B, Lyu K-S et al. Association of polymorphisms in C1orf106, IL1RN, and IL10 with post-induction infliximab trough level in Crohn’s disease patients. Gastroenterol Rep (Oxf) 2019, 10.1093/gastro/goz056.
24. Morita Y, Bamba S, Takahashi K et al. Prediction of clinical and endoscopic responses to anti-tumor necrosis factor-alpha antibodies in ulcerative colitis. Scand J Gastroenterol 2016;51:934–41.
25. Lee KM, Jeen YT, Cho JY et al. Efficacy, safety, and predictors of response to infliximab therapy for ulcerative colitis: a Korean multicenter retrospective study. J Gastroenterol Hepatol 2013;28:1829–33.
26. Ferrante M, Vermeire S, Katsanos KH et al. Predictors of early response to infliximab in patients with ulcerative colitis. Inflamm Bowel Dis 2007;13:123–8.
27. Burke KE, Khalili H, Garber JJ et al. Genetic markers predict primary nonresponse and durable response to anti-tumor necrosis factor therapy in ulcerative colitis. Inflamm Bowel Dis 2018;24:1840–8.
28. Papay P, Ignjatovic A, Karmiris K et al. Optimising monitoring in the management of Crohn’s disease: a physician’s perspective. J Crohns Colitis 2013;7:653–69.