World Journal of Gastroenterology

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World J Gastroenterol 2017 October 28; 23(40): 7265-7273

DOI: 10.3748/wjg.v23.i40.7265

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Genetic associations with adverse events from anti-tumor necrosis factor therapy in inflammatory bowel disease patients

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Author contributions: Lew D collected and analyzed the data, and drafted the manuscript; Yoon SM and Robbins L helped collect the data and edit the manuscript; Yan X and Li D helped with the technical and statistical analysis; Liu Z and Haritunians T helped analyze the data and edit the manuscript; McGovern DPB designed and supervised the study, and revised the manuscript for important intellectual content; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Cedars-Sinai Institutional Review Board (IRB #3358).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: DPBM reports consulting for Janssen, UCB, Pfizer, Celgene, and Merck.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: August 5, 2017
Peer-review started: August 5, 2017
First decision: August 14, 2017
Revised: August 25, 2017
Accepted: September 13, 2017
Article in press: September 13, 2017
Published online: October 28, 2017

Abstract

AIM

To study the type and frequency of adverse events associated with anti-tumor necrosis factor (TNF)

therapy and evaluate for any serologic and genetic associations.

METHODS

This study was a retrospective review of patients attending the inflammatory bowel disease (IBD) centers at Cedars-Sinai IBD Center from 2005-2016. Adverse events were identified *via* chart review. IBD serologies were measured by ELISA. DNA samples were genotyped at Cedars-Sinai using Illumina Infinium Immunochipv1 array per manufacturer's protocol. SNPs underwent methodological review and were evaluated using several SNP statistic parameters to ensure optimal allele-calling. Standard and rigorous QC criteria were applied to the genetic data, which was generated using immunochip. Genetic association was assessed by logistic regression after correcting for population structure.

RESULTS

Altogether we identified 1258 IBD subjects exposed to anti-TNF agents in whom Immunochip data were available. 269/1258 patients (21%) were found to have adverse events to an anti-TNF-α agent that required the therapy to be discontinued. 25% of women compared to 17% of men experienced an adverse event. All adverse events resolved after discontinuing the anti-TNF agent. In total: *n* = 66 (5%) infusion reactions; n = 49 (4%) allergic/serum sickness reactions; *n* = 19 (1.5%) lupus-like reactions, *n* = 52 (4%) rash, *n* = 18 (1.4%) infections. In Crohn's disease, IgA ASCA (*P* = 0.04) and IgG-ASCA (*P* = 0.02) levels were also lower in patients with any adverse events, and anti-I2 level in ulcerative colitis was significantly associated with infusion reactions (*P* = 0.008). The logistic regression/human annotation and network analyses performed on the Immunochip data implicated the following five signaling pathways: JAK-STAT (Janus Kinase-signal transducer and activator of transcription), measles, IBD, cytokine-cytokine receptor interaction, and toxoplasmosis for any adverse event.

CONCLUSION

Our study shows 1 in 5 IBD patients experience an adverse event to anti-TNF therapy with novel serologic, genetic , and pathways associations.

Key words: Genetic associations; Inflammatory bowel disease; Anti-tumor necrosis factor; Adverse events

Core tip: Tumor necrosis factor-α (TNF-α) plays a key role in the development and progression of inflammatory bowel disease (IBD). Anti-TNF therapy is highly efficacious in treating IBD patients, but many experience adverse events. Few studies have evaluated factors associated with adverse events to anti-TNF therapy. In this study, we found some genetic associations and pathways that are enriched for genes associated with the development of adverse events. Future studies will need to confirm these findings as the ability to identify subjects at high risk may help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

Lew D, Yoon SM, Yan X, Robbins L, Haritunians T, Liu Z, Li D, McGovern DPB. Genetic associations with adverse events from anti-tumor necrosis factor therapy in inflammatory bowel disease patients. *World J Gastroenterol* 2017; 23(40): 7265-7273 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i40/7265.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i40.7265

INTRODUCTION

Tumor necrosis factor-α (TNF-α) plays a key role in the development and progression of inflammatory bowel disease (IBD)[1-3]. While anti-TNF therapy is an effective therapeutic option for IBD patients[1,4,5], response to these agents is highly heterogeneous and a high proportion of patients either fail initial induction therapy or lose response during maintenance therapy[6-8]. Predicting response to these agents has been studied extensively by evaluating a multitude of factors including potential genetic components[7], but an important addition would be the ability to predict the development of adverse events associated with these agents including: infusion reactions; infections; rash; allergic reactions; serum sickness like reactions; and lupus-like reactions[9-11]. Minimizing the risks is important to increase patient compliance and improve response to therapy, and will also become more important as physicians struggle with decisions around where to position biologic therapies as therapeutics targeting novel mechanisms become available[12,13].

Currently, there are few studies designed to determine factors associated with adverse events to anti-TNF-α therapy. The objectives of this study were to describe the type and frequency of adverse events associated with anti-TNF-α therapy in a large cohort and evaluate for any serologic and genetic associations.

MATERIALS AND METHODS

Study population

This study was a retrospective review of patients attending the IBD centers at Cedars-Sinai IBD Center from 2005-2016. Patients included in the study were

those that had given consent, had available genotype data, carried a diagnosis of IBD (Crohn's disease, ulcerative colitis, or IBDU), and who had been treated with anti-TNF-α agents (infliximab, adalimumab, certolizumab pegol). All research-related activities were approved by the Cedars-Sinai Medical Center Institutional Review Board (IRB #3358).

Data gathering

Detailed clinical information for each patient was obtained *via* chart review. Clinical information included age at disease diagnosis, type of IBD (CD, UC, or IBDU), gender, and type of anti-TNF-α agent used. All patients were seen by gastroenterologists, experienced in managing patients with IBD treated with anti-TNF agents, at the IBD centers at Cedars-Sinai Medical Center, Los Angeles.

Adverse events

Adverse events were identified *via* chart review by evaluating the "Allergies" section and the progress notes written by the gastroenterologist. Potential adverse events include infusion reactions, serum sickness-like reactions, drug-induced lupus, rash, infections, and non-specific symptoms (arthralgias, shortness of breath, rash, *etc*). An infusion reaction was defined as any significant adverse experience that occurred during or within two hours of infusion[14]. An allergic or a serum sickness-like reaction was defined clinically as the occurrence of myalgias, arthralgias, fever, or rash within 1-14 d after reinfusion of infliximab[15].

The likelihood of a causal relationship for each adverse event was determined based on the assessment of the gastroenterologist as documented in the progress note and as evidenced by the following: time elapsed between a dose and adverse event, resolution of the adverse event when the therapy was discontinued, and return of the adverse event if the therapy was resumed[16].

Serological analysis

IBD serologies (ANCA, anti-nuclear cytoplasmic antibodies; anti-CBir1, anti-flagellin; anti-I2, anti-*Pseudomonas fluorescens*-associated sequence I2; anti-OmpC, anti-outer membrane porin C; ASCA, anti-*Saccharomyces cerevisiae* antibodies) were measured by enzyme-linked immunosorbent assay (ELISA) as previously described[17]. Results were expressed as ELISA units (EU/mL) relative to Cedars-Sinai Medical Center laboratory or a Prometheus laboratory standard derived from a pool of patient sera with well-characterized disease found to have reactivity to these antigens. All assays were performed in a blinded fashion.

Genotype data

DNA samples were genotyped at Cedars-Sinai using Illumina Infinium Immunochipv1 array per manufacturer's protocol (Illumina, San Diego, CA, United States). Average genotyping call rate for samples that passed quality control was 99.8%; average replicate concordance and average heritability rates were > 99.99% and 99.94%, respectively. Single-nucleotide polymorphisms (SNPs) underwent methodological review and were evaluated using several SNP statistic parameters to ensure optimal allele-calling[18].

Statistical analysis

χ^2 test and logistic regression were performed to identify demographic and clinical characteristics associated with development of adverse events. For continuous variables with skewed distribution (*e.g.*, serology levels), Wilcox test signed rank test was performed. SNPs association with adverse events was evaluated using PLINK. Principal components (PCs) from population stratification analysis were included in the PLINK analysis to control for potential confounding[19]. Two-sided *P*-value of 0.05 was considered statistically significant.

Genetic pathway, and network analyses

For any reaction, infusion reactions, and allergic reactions, the logistic regression/human annotation and network analysis was performed with statistically significant SNPs ($P < 0.001$). These SNPs were first annotated into corresponding genes, and the genes were further analyzed with multiple biological functional databases including human protein reference databases (http://www.hprd.org), Reactome, NCI/Nature pathway interaction database and others. The final networks were then constructed form the known interactions from any of these databases. Pathways and gene set enrichment analysis was performed with STRING (http://string-db.org/) and cytoscape (http://www.cytoscape.org).

RESULTS

Patient demographics and characteristics

1258 IBD (954 CD patients, 260 UC, 44 IBDU) patients qualified for this study. The average age of onset was 25.7 years and, and the overwhelming majority were of European ancestry.

Adverse events

A total of 269/1258 patients (21%) were found to have experienced an adverse event. The different

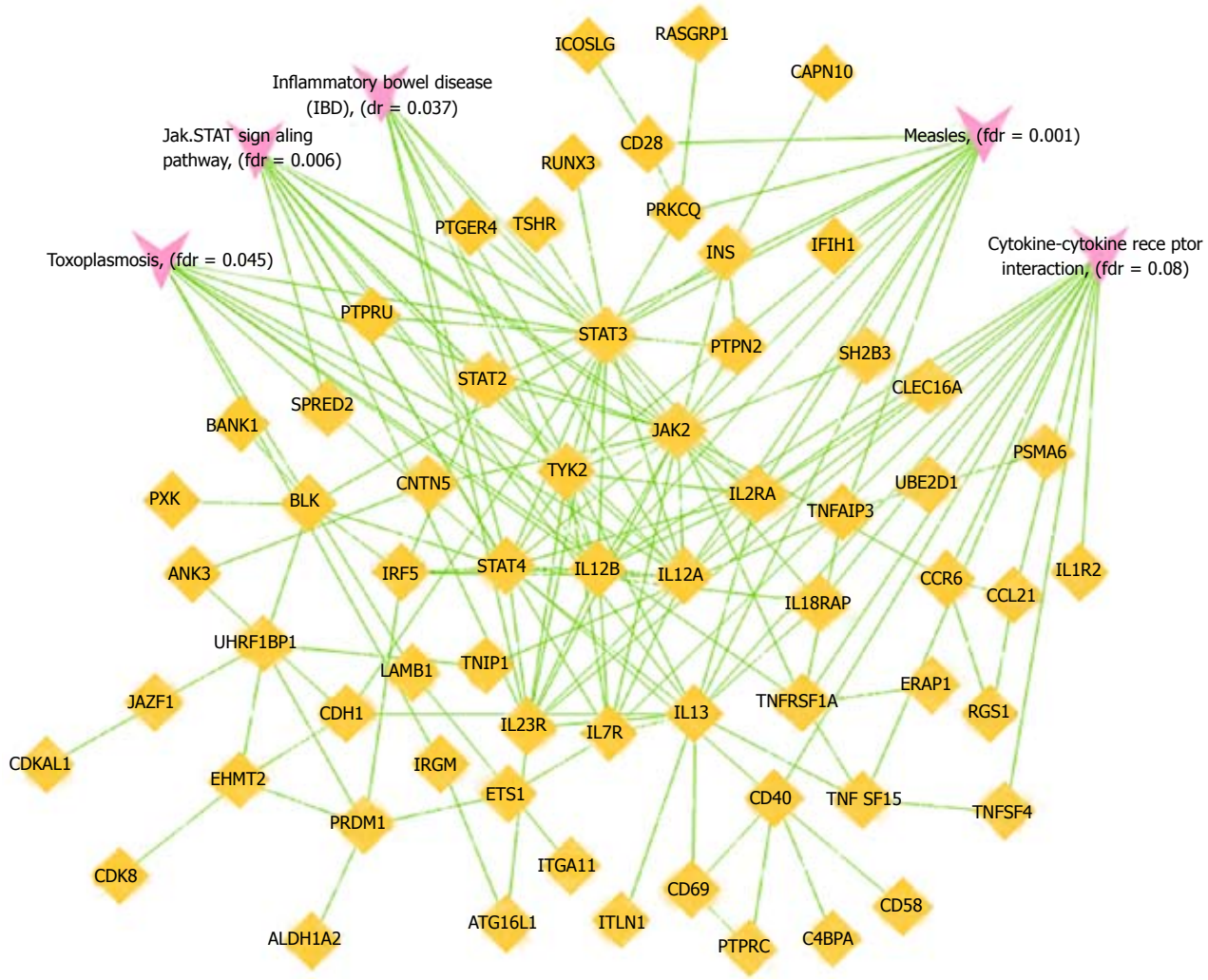

Figure 1 Network analyses of allergic reactions to anti-tumor necrosis factor agents.

types of adverse events were similar among women and men, except for lupus-like reactions and rashes, which were both more commonly seen in women (Table 1).

Serology

In CD patients we observed that IgA ASCA+/- was associated with a lower risk of developing any adverse event (OR = 0.68, *P* = 0.047), while IgG ASCA+/- and total ASCA+/- show a similar trend and borderline association respectively (OR = 0.72 and 0.70, *P* = 0.09 and 0.05, respectively). IgA ASCA (*P* = 0.04) and IgG ASCA (*P* = 0.02) levels were also lower in patients with any adverse events (Table 2). Anti-I2 level in UC was significantly associated with infusion reactions (*P* = 0.008) (Table 2). No other associations were seen with IBD-associated serologies (data not shown).

Genetic analysis

IBD-associated SNPs that achieved a nominal level of significance with adverse events are shown in Table 3. For any reaction, infusion reactions, and allergic reactions, the logistic regression/human annotation and network analyses performed on the Immunochip data implicated the following five signaling pathways: JAK-STAT (Janus Kinase-signal transducer and activator of transcription), Measles, IBD, Cytokine-cytokine receptor interaction, and Toxoplasmosis (Table 4 and Figure 1). After False Discovery Rate correction, all associations remained statistically significant except for the Cytokine-cytokine receptor interaction for infusion and allergic reactions.

DISCUSSION

In our cohort approximately 1 in 5 IBD patients experienced adverse events to anti-TNFs that eventually led to the discontinuation of the therapy in keeping with the current literature, although most studies only report the presence or not of adverse events and do not comment on whether patients had to

Table 1 Adverse events based on type of inflammatory bowel disease and gender *n* (%)

Clinical traits	All adverse events	Infusion reactions	Allergic reactions	Lupus-like reactions	Rash	Other
Type of IBD						
Crohn's disease (*n* = 954)	220 (23)	52 (5)	45 (5)	14 (1)	40 (4)	69 (7)
Ulcerative colitis (*n* = 260)	42 (16)	14 (5)	4 (2)	4 (2)	10 (4)	10 (4)
IBDU (*n* = 44)	7 (16)	0 (0)	0 (0)	1 (2)	2 (5)	4 (9)
Total	269 (21)	66 (5)	49 (4)	19 (1.5)	52 (4)	83 (7)
Gender						
Male (*n* = 624)	108 (17)	28 (4)	24 (4)	3 (0.5)	17 (3)	36 (6)
Female (*n* = 634)	161 (25)	38 (6)	25 (4)	16 (3)	35 (6)	47 (7)

All values expressed as *n* (%). IBD: Inflammatory bowel disease.

Table 2 Serological associations with anti-tumor necrosis factor adverse reactions in patients with ulcerative colitis and Crohn's disease (anti-I2, anti-*Pseudomonas fluorescens*-associated sequence I2; ASCA, anti-Saccharomyces cerevisiae antibodies)

IBD type	Adverse event	Serological marker	Serology levels in positive (U/mL)	Serology levels in negative (U/mL)	*P* value
CD	Any	IgA ASCA	7	10	0.040
CD	Any	IgG ASCA	18	26.5	0.020
UC	Infusion	Anti-I2	0	7	0.008

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

Table 3 Inflammatory bowel disease-associated single nucleotide polymorphisms associated with different type of adverse events

Adverse event	Risk allele	SNP	Gene (s) of interest	*P* value	OR (95%CI)
Infusion	C	rs6740462	*SPRED2*	0.003	0.4 (0.2-0.7)
Infusion	G	rs1182188	*GNA12*	0.007	1.8 (1.2-2.6)
Infusion	G	rs10061469	*TMEM174, FOXD1*	0.010	0.5 (0.3-0.9)
Infusion	A	rs477515	*HLA-DRB1*	0.010	1.7 (1.1-2.5)
Allergic	A	rs4692386	*SMIM20, RBPJ*	0.010	0.5 (0.3-0.9)
Allergic	A	rs10761659	*ZNF365*	0.010	0.6 (0.3-0.9)
Lupus-like	G	rs13407913	*ADCY3*	0.003	3.5 (1.6-7.9)
Lupus-like	C	rs10051722	*CHSY2, HINT1*	0.010	2.7 (1.2-5.7)
Rash	A	rs1363907	*ERAP2*	0.003	3.0 (1.5-6.2)
Rash	G	rs11010067	*PARD3*	0.003	0.2 (0.1-0.6)
Rash	C	rs7746082	*PREP*	0.005	2.7 (1.3-5.3)
Any	C	rs6740462	*SPRED2*	0.0007	0.6 (0.5-0.8)
Any	C	rs10774482	*ERC1*	0.003	1.4 (1.1-1.8)

SNP: Single nucleotide polymorphisms.

discontinue[20]. The incidence of serious lupus-like reactions requiring the discontinuation of anti-TNFs was found to be 1.1%[21], which was comparable to that seen in our population of 1.5%. To our knowledge, this is the largest study examining adverse events with anti-TNF agents.

We identified a number of genetic associations with known IBD loci including two (*HLA-DRB1* and *ERAP2* [endoplasmic reticulum aminopeptidase 2]) that are associated with a number of immune-mediated diseases as well as IBD and also, in the case of *HLA-DRB1*, with the development of extra-intestinal manifestations in IBD[22-24]. Furthermore, both are involved in peptide presentation by HLA molecules[25,26]. We also observed associations at other IBD genes including *ZNF365,* a transcription factor in maintaining genomic stability during DNA replication in the brain, heart, lung, pancreas, small intestine and colon[27,28]. Our genetic findings also implicated genes that maintain colonic wall permeability including *SPRED* (Sprouty-related EVH1 domain-containing protein) and *PARD3* (Partitioning defective 3 homolog)[29,30]. In addition, *GNA12* (Guanine nucleotide-binding protein alpha-12), a modulator of different transmembrane signaling systems, has also been implicated in the loss of barrier integrity[31]. Our pathway analyses strongly implicated

Table 4 Pathway analyses from genetic associations with adverse events from immunochip analyses

Type of adverse event	Pathway	Number of genes	*P* value	*P* value (Bonferroni)
Any	JAK-STAT signaling pathway	13	3.98×10^{-6}	7.96×10^{-4}
Any	Measles	12	8.87×10^{-6}	0.0018
Any	IBD	8	3.05×10^{-5}	0.0061
Any	Cytokine-cytokine receptor interaction	16	5.03×10^{-5}	0.0100
Any	Toxoplasmosis	10	5.49×10^{-5}	0.0110
Infusion	JAK-STAT signaling pathway	12	3.68×10^{-5}	0.0074
Infusion	Measles	12	8.24×10^{-6}	0.0016
Infusion	IBD	7	2.11×10^{-4}	0.0420
Infusion	Cytokine-cytokine receptor interaction	14	4.98×10^{-4}	0.0990
Infusion	Toxoplasmosis	11	9.02×10^{-6}	0.0018
Allergic	JAK-STAT signaling pathway	12	2.96×10^{-5}	0.0060
Allergic	Measles	12	6.6×10^{-6}	0.0010
Allergic	IBD	7	1.84×10^{-4}	0.0370
Allergic	Cytokine-cytokine receptor interaction	14	4.02×10^{-4}	0.0800
Allergic	Toxoplasmosis	9	2.25×10^{-4}	0.0450

IBD: Inflammatory bowel disease.

five signaling pathways including JAK-STAT signaling pathway, Cytokine-cytokine receptor interaction pathway, Measles signaling pathway, Toxoplasmosis signaling pathway, and the IBD signaling pathway. The network analyses for allergic reactions (Figure 1) show a number of key nodes including *TYK2, BLK* and *IL13*, which have previously been shown to be associated with allergic susceptibility[32-34].

IBD serologies (ANCA, anti-CBir1, anti-I2, anti-OmpC, and ASCA) can distinguish CD from UC, risk stratify IBD patients, and also predict postoperative complications and occur as a result of an aberrant or exaggerated response to commensal flora[35]. The association with ASCA and I2 are interesting. Perhaps these markers identify patients with a predilection towards small bowel involvement. Patients with colonic disease tend to respond less to anti-TNFs or require higher doses[8,36] and, perhaps therefore, these patients are more likely to develop antibodies or reactions to anti-TNFs. Further studies will be needed to confirm these borderline associations.

There are several potential limitations of this study including, the relatively small sample size and the retrospective nature of the study (despite it being the largest of its kind to date). Additionally, we did not have information on anti-drug antibody formation as the majority of these patients developed adverse events prior to the widespread use of these parameters in clinical practice. It is also important to note that our study population was predominantly of European ancestry. While IBD is rising in non-Europeans, the highest prevalence is still seen in European ancestry populations. For this reason, and the location of Cedars-Sinai Medical Center in west Los Angeles, the majority of our patients are "European". Previous work have shown ethnic differences in genetic associations with adverse events[37], and a study similar to this one should be performed for other ethnic groups.

In conclusion, our study revealed that approximately 1 in 5 IBD patients experienced an adverse event to anti-TNF therapies that required cessation of therapy. The majority of these were infusion/allergic reactions but approximately 1 in 30 women will develop a lupus-like reaction and we also observed other serious adverse events including pancreatitis and vascultitis but these were rare. We have demonstrated some genetic associations and pathways that are enriched for genes associated with development adverse events. Future studies will need to confirm these findings as the ability to identify subjects at high risk may help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

ATRICLE HIGHLIGHTS

Research Background

Tumor necrosis factor (TNF) inhibitors are highly efficacious in treating inflammatory bowel disease (IBD). Response to these agents is highly heterogenous, and there have been a multitude of studies aimed at predicting the response to these agents. An important addition is the ability to predict the development of adverse events associated with these agents such as infusion reactions, infections, or rash. Minimizing the risk is important to increase patient compliance and improve response to therapy.

Research motivation

Recognizing the type and frequency of adverse events to anti-TNF therapy, and the potential genetic and serologic associations can help identify subjects at high risk, and may help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

Research objectives

The objectives of this study were to describe the type and frequency of adverse

events associated with anti-TNF-α therapy in a large cohort and evaluate for any serologic and genetic associations. The significance of realizing these objectives is that it can identify subjects at high risk for developing adverse events and can help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

Research methods

This study was a retrospective review, and detailed clinical information was collected *via* manual chart review. χ^2 test and logistic regression were performed to identify demographic and clinical characteristics associated with development of adverse events.

The serological data was measured by ELISA assay at Cedars-Sinai, which was performed in a blinded fashion, and analyzed with Wilcox test signed rank test.

DNA samples were genotyped at Cedars-Sinai using Illumina Infinium Immunochipv1 array per manufacturer's protocol (Illumina, San Diego, CA, United States). Average genotyping call rate for samples that passed quality control was 99.8%; average replicate concordance and average heritability rates were > 99.99% and 99.94%, respectively. Single-nucleotide polymorphisms (SNPs) underwent methodological review and were evaluated using several SNP statistic parameters to ensure optimal allele-calling. SNPs association with adverse events was evaluated using PLINK, with two-sided p-value of 0.05 was considered statistically significant.

For any reaction, infusion reactions, and allergic reactions, the logistic regression/human annotation and network analysis was performed with statistically significant SNPs ($P < 0.001$). These SNPs were first annotated into corresponding genes, and the genes were further analyzed with multiple biological functional databases. The final networks were then constructed form the known interactions from any of these databases.

The research methods described above are standard for a retrospective review analyzing genetic and serologic data.

Research results

About 1 in 5 patients were found to have adverse events to an anti-TNF-α agent that required the therapy to be discontinued. All adverse events resolved after discontinuing the anti-TNF agent. The majority of patients developed infusion reactions. In CD patients we observed that IgA ASCA +/- was associated with a lower risk of developing any adverse event. IgA ASCA and IgG ASCA levels were also lower in patients with any adverse events. Anti-I2 level in UC was significantly associated with infusion reactions. The authors identified a number of genetic associations with known IBD loci including *HLA-DRB1, ERAP2, ZNF365*. Their pathway analyses strongly implicated JAK-STAT signaling pathway, Cytokine-cytokine receptor interaction pathway, Measles signaling pathway, Toxoplasmosis signaling pathway, and the IBD signaling pathway. The network analyses for allergic reactions showed a number of key nodes including *TYK2, BLK* and *IL13*, which have previously been shown to be associated with allergic susceptibility.

They have demonstrated some novel genetic associations and pathways that are enriched for genes associated with development adverse events. Future studies should be performed to confirm our results, and incorporate other ethnic groups besides European ancestry, and include data on anti-drug antibody formation.

Research conclusions

The genetic and serologic associations found in concordance with adverse events to anti-TNF therapy. This is the first study to evaluate and describe these associations. There are potentially genetic and serologic associations with adverse events to anti-TNF therapy that can help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

Current studies describe in great detail the efficacy of anti-TNF therapy and the ability to predict response to therapy. However, current studies are lacking in evaluating the ability to predict the development of adverse events. The results from this study reveal that there indeed are genetic and serologic associations with anti-TNF therapy that can potentially be targeted to prevent or avoid these adverse events in the future. The new hypothesis proposed by this study is that there serologic and genetic associations with anti-TNF therapy.

The methods used in this study were similar to other retrospective studies analyzing genetic and serologic data. Manual chart review was performed to generate detailed clinical information; ELISA assay was performed to gather serologic data; and genetic data was generated using Illumina Infinium Immunochipv1 array. χ^2 test and logistic regression were performed to identify demographic and clinical characteristics associated with development of adverse events; serological data were analyzed with Wilcox test signed rank test; and SNPs association with adverse events were evaluated using PLINK, with two-sided *P*-value of 0.05 considered statistically significant.

The genetic and serologic associations found in concordance with adverse events to anti-TNF therapy are novel and have not been described elsewhere. This study confirmed that there are genetic and serologic associations with adverse events from anti-TNF therapy. Identifying the potential factors associated with adverse events from anti-TNF therapy can help clinicians anticipate and therefore prevent or avoid these adverse events in the future.

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P- Reviewer: Gassler N, Sebastian S, Sergi CM, Zhulina Y
S- Editor: Gong ZM **L- Editor**: A **E- Editor**: Ma YJ

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ISSN 1007-9327