Tohoku J. Exp. Med., 2023, **260**, 263-271

Predictive Values of Blood Type I and Type II Interferon Production for Disease Activity and Clinical Response to TNF-*α* Blocking Therapy in Patients with Ankylosing Spondylitis

Yulan Hu,[1] Bo Lou,[1] Zhonghua Jiang[1] and Chunchu Yu[2]

[1]Department of Endocrinology, the First People's Hospital of Linping District, Hangzhou, Zhejiang, China
[2]Obstetrical Department, the First People's Hospital of Linping District, Hangzhou, Zhejiang, China

Tumor necrosis factor-*α* (TNF-*α*) blocking therapy is recommended to treat ankylosing spondylitis for patients who fail to respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Herein, we attempt to dissect whether blood type I and II interferon (IFN) production can be predictive of ankylosing spondylitis progression and treatment response to the tumor necrosis factor inhibitor (TNFi). A total of 50 ankylosing spondylitis patients receiving originator TNFi with a 6-month period were retrospectively analyzed. The patients who reached the Assessment of SpondyloArthritis international Society 40 (ASAS40) response at the 6-month interval were classified as responders (n = 29) to TNFi treatment, otherwise as non-responders (n = 21). The serum type I IFN activity, and the serum levels of IFN-*α* and IFN-*γ* in the patients at baseline were notably greater than the healthy controls. Pearson correlation analysis showed positive correlations in the patients between the serum type I IFN activity or the serum levels of IFN-*α* and IFN-*γ*, and BASDAI scores, $ASDAS_{CRP}$ or pro-inflammatory factor production. The responders were demonstrated with reduced serum type I IFN activity concomitant with lower serum levels of IFN-*α* and IFN-*γ* compared to the non-responders after anti-TNF treatment. The serum type I IFN activity, and the serum levels of IFN-*α* and IFN-*γ* used as a test to predict responders and non-responders to anti-TNF treatment produced an area under the curve (AUC) of 0.837, 0.814, and 0.787, respectively. In conclusion, the study demonstrates that blood type I and II IFN production may be correlated with disease activity, inflammatory cytokine production, and indicative of unsatisfying response to TNFi treatment in ankylosing spondylitis patients.

Keywords: ankylosing spondylitis; interferon-*γ*; tumor necrosis factor inhibitor; type I interferon; type II interferon
Tohoku J. Exp. Med., 2023 July, **260** (3), 263-271.
doi: 10.1620/tjem.2023.J033

Introduction

Ankylosing spondylitis represents the prototype of the spondyloarthritides that primarily affect the sacroiliac joints and the axial skeleton (Robinson et al. 2021). Ankylosing spondylitis is insidiously progressive and has a delayed diagnosis many years after onset of symptoms, which, if untreated, may progress to severe structural damage of the spine and poor quality of life (Proft and Poddubnyy 2018; Ritchlin and Adamopoulos 2021). The pathogenic mechanisms underlying ankylosing spondylitis is likely multifactorial and remains poorly understood by now (Voruganti and Bowness 2020), but there is a growing appreciation for the role of human leukocyte antigen B27 (HLA-B27) genotype in ankylosing spondylitis (Mauro et al. 2021). The disease usually begins at 30 years of age (Lee et al. 2022b), and the HLA-B27-positive individuals presented with ankylosing spondylitis almost 5 years earlier than the HLA-B27-negative patients (Navid et al. 2021). The prevalence of ankylosing spondylitis in China ranges from 0.20% to 0.42%, with 88.8-89.4% of HLA-B27-positive individuals (Zhang et al. 2022). Internationally approved medications for ankylosing spondylitis include nonsteroidal anti-inflammatory drugs (NSAIDs) which are still the first-line pharmacological therapy for ankylosing spondylitis patients and biological disease-modifying anti-rheumatic drugs (DMARDs) for those with limited response to NSAIDs, such as tumor necrosis factor (TNF) inhibitors (TNFi),

Received March 14, 2023; revised and accepted April 8, 2023; J-STAGE Advance online publication April 20, 2023
Correspondence: Yulan Hu, Department of Endocrinology, the First People's Hospital of Linping District, No. 369, Yingbin Road, Nanyuan Street, Linping District, Hangzhou, Zhejiang 311100, China.
e-mail: claudiahuyulan@163.com

IL-17 inhibitors, and Janus kinase inhibitors (JAKi) (Tahir 2018; Webers et al. 2023). However, a non-negligible proportion of ankylosing spondylitis patients fail to achieve desired treatment goals including low disease activity to biological DMARDs (Klavdianou et al. 2021). This failure has raised identification of molecular biomarkers to offer guidance for making alternative treatment decision and improving the therapeutic success for ankylosing spondylitis patients.

Interferons (IFNs) fall in three distinct types designated as type I, type II, and type III IFNs according to their receptor usage, structural features and biological activities (Walter 2020). The type I IFN family is a multigene family encoding pleiotropic cytokines including numerous highly conserved IFN-α subtypes, a single IFN-β, and several others (IFN-ε and IFN-ω), which have been implicated in the host's innate defense against viral infection (McNab et al. 2015). The type II IFN only contains a single gene product, IFN-γ, that is predominantly produced by T cells and natural killer (NK) cells and can act on a broad array of cell types that express the IFN-γ receptor (Pollard et al. 2013). The type III IFN family are the latest addition to the IFN family and encompasses IFNλ1, λ2 and λ3 and the recently identified IFNλ4, which are responsible for immune host defense against viral infection at endothelial and epithelial barriers (Manivasagam and Klein 2021). IFN regulated genes (IRGs), a group of genes associated with type 1 IFN signaling, were previously reported to be associated with clinical response to anti-TNF treatment in ankylosing spondylitis patients (Harrison et al. 2021). IFN-γ was found to function as the strongest activating factor inducing the unfolded protein response in HLA-B27-expressing cells, which may participate in the pathogenesis of spondyloarthropathies (Feng et al. 2012). Ankylosing spondylitis patients were demonstrated with notably increased levels of Th1 cytokines, IFN-γ and IFN-γ-inducible protein-10 (IP-10/CXCL10), compared to healthy controls, and a positive correlation between IP-10 and TNF-α as well as decreased levels of both Th1 and Th2 chemokines after TNF-α blocking therapy were observed (Wang et al. 2016). Considering the pathological importance of type I and II IFN production in ankylosing spondylitis, we recruited 50 patients with ankylosing spondylitis receiving originator TNFi with a 6-month period to determine the predictive potential of blood type I and II IFN production for clinical response to anti-TNFi therapy.

Methods

Patient selection

This prospective study consecutively included 50 patients who were treated with originator TNFi for active ankylosing spondylitis and followed up for 6 months from the first anti-TNF therapy at the First People's Hospital of Linping District during the period of 2021-2022. Inclusion criteria were: i) the ankylosing spondylitis diagnosis confirmed by the same rheumatologist according to documented radiographic sacroiliitis, fulfilling the classification criteria issued by the Assessment of SpondyloArthritis international Society (ASAS); ii) symptom duration of more than 3 months; iii) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 4; iv) Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDASCRP) > 2.1; v) no treatment history of biological DMARDs such as anti-TNF agents, anti-IL-6 agents, and anti-IL-17 agents; and vi) aged 18 years or older. Exclusion criteria were: i) antibiotics prescribed for in the previous 3 months; ii) long-term intake of anti-inflammatory medications; iii) current ongoing rheumatoid arthritis or other inflammatory diseases, such as active/symptomatic Crohn's disease or ulcerative colitis; iv) any current ongoing pulmonary, hepatic, renal, hematological, neurological, neoplastic diseases, or psychiatric abnormalities; and v) pregnancy (tested with β-human chorionic gonadotropin test) or breastfeeding. Age- and sex-matched healthy volunteers were recruited as the control and their recruitment applied the same exclusion criteria as the included ankylosing spondylitis patients. The number of population controls was 50. The study protocols were approval by the Ethics Committee of the First People's Hospital of Linping District. The study was in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

Disease severity assessment

The disease activity of included ankylosing spondylitis patients was examined by applying a series of scales including BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), total back pain, Patient's Global Assessment of Disease Activity (PGADA), and ASDASCRP. The BASDAI, BASFI, total back pain, and PGADA were assessed by using a 10-cm visual analogue scale.

Treatment protocols and clinical response

All patients included in this study received 40 mg adalimumab (Abbott Laboratories, Abbott Park, IL, USA) as TNFi treatment by subcutaneous injections every month (M0, M1, and M2) followed by further injections every 2 months (M4 and M6) across a 6-month period in total. The patients who achieved an ASAS 40% improvement in disease activity (ASAS40) at the M4 were regarded as responders to TNFi treatment, otherwise as non-responders.

Blood sample collection

Included patients were requested to provide peripheral blood after overnight fasting at baseline (before starting anti-TNF treatment) and 6 months after anti-TNF treatment, and from healthy controls at their physical examination, respectively. The peripheral blood samples were then placed into pyrogen/endotoxin-free tubes, followed by centrifugation at 2,000 $\times g$ for 10 min, and then the serum was obtained.

Reporter cell assay for serum type I interferon activity

Serum type I IFN activity was determined in the reporter cell assay. In brief, the reporter cells WISH (#CCL-25, ATCC, Rockville, MD, USA) were exposed to 50% patient sera for 6 h and then lysed. The Trizol reagents (Invitrogen, Carlsbad, CA, USA) were used for total RNA isolation from the WISH cells, and the PrimeScript RT Reagent kit (Takara, Dalian, China) was used for cDNA synthesis. *MX1*, *PKR* and *IFIT1* are known to be canonical type I IFN-induced genes, and their expressions were quantified by qPCR (Table 1 lists the primer sequences) using the SYBR Master Mixture (Takara, Tokyo, Japan) and the LightCycler 480 II System (Roche Diagnostics, Indianapolis, IN, USA). GADPH was used for loading control. The relative expressions of *MX1*, *PKR* and *IFIT1* in ankylosing spondylitis patient sera were normalized to those in healthy control sera and then summed to a score determining the ability of sera to induce IFN-induced gene expression, namely serum type I IFN activity.

Detections of circulating IFNs and inflammatory cytokines

The serum samples were submitted to commercially available human ELISA kits for IFN-α (ab213479, Abcam, Cambridge, UK), IFN-γ (ab174443, Abcam), TNF-α (ab181421, Abcam), IL-1β (ab214025, Abcam) and IL-6 (ab178013, Abcam). The serum samples were also allowed to measure the concentration of C-reactive protein (CRP) by turbidimetric method with Automatic Biochemical Instruments.

Statistical analysis

Continuous data were determined to fit the normal distribution by using the Shapiro-Wilk test. In the case when the normal distribution was satisfied, continuous data were obtained using mean ± standard deviation (SD). Difference for data from the baseline (M0) to different time points (M1, M2, M4 and M6) was determined by using the one-way analysis of variance (ANOVA), and these differences were compared between responders and non-responders by using the two-way ANOVA. Difference between ankylosing spondylitis patients and healthy controls, responders and non-responders was assessed by using the unpaired t-test. The correlation of the serum type I IFN activity and the serum levels of IFN-α and IFN-γ, with disease severity and pro-inflammatory factor production of ankylosing spondylitis patients was assessed by Pearson correlation test. Two-tail tests of statistical significance were used and performed using SPSS 24.0 (IBM, Armonk, NY, USA), with the significance level set at $p < 0.05$.

Results

Induction of type I and II IFN production in ankylosing spondylitis

The functional assay for serum type I IFN activity showed that the summed scores in patients with ankylosing spondylitis at baseline (before beginning TNFi treatment) were notably higher than the healthy controls ($p < 0.001$, Fig. 1A). Data obtained from ELISA detection also showed that the serum levels of IFN-α and IFN-γ were increased in patients with ankylosing spondylitis at baseline than in the healthy controls ($p < 0.001$, Fig. 1B, C). Among 50 patients with ankylosing spondylitis, there were 32 patients positive for HLA-B27 and 18 patients negative for HLA-B27. The serum type I IFN activity, and the serum levels of IFN-α and IFN-γ did not significantly differ between HLA-B27-positive and HLA-B27-negative patients ($p > 0.05$, Fig. 1D-F). These data suggest that induction of type I and II IFN production may be implicated in the immunopathology of ankylosing spondylitis.

Association between type I and II IFN production and disease activity in ankylosing spondylitis

After Pearson correlation analysis, it was found that the serum type I IFN activity shared positive correlations with BASDAI scores ($r=0.732$, $p< 0.0001$), $ASDAS_{CRP}$ ($r= 0.693$, $p< 0.0001$), and the serum level of IFN-α ($r= 0.573$, $p< 0.0001$) of ankylosing spondylitis patients (Fig. 2A). The serum level of IFN-α was positively correlated with BASDAI scores ($r=0.711$, $p< 0.0001$) and $ASDAS_{CRP}$ ($r = 0.562$, $p< 0.0001$) of ankylosing spondylitis patients (Fig. 2B). The serum level of IFN-γ were positively correlated with BASDAI scores ($r= 0.701$, $p< 0.0001$) and $ASDAS_{CRP}$ ($r = 0.670$, $p< 0.0001$) of ankylosing spondylitis patients (Fig. 2C). However, no significant correlation of the serum type I IFN activity or the serum levels of IFN-α and IFN-γ was observed with BASFI scores, total back pain scores, or

Table 1. Primer sequences for qPCR.

Target	Primer sequence (5'-3')
MX1	Sense: 5'-TACCAGGACTACGAGATTG-3'
	Antisense: 5'-TGCCAGGAAGGTCTATTAG-3'
PKR	Sense: 5'-CTTCCATCTGACTCAGGTTT-3'
	Antisense: 5'-TGCTTCTGACGGTATGTATTA-3'
IFIT1	Sense: 5'-CTCCTTGGGTTCGTCTATAAATTG-3'
	Antisense: 5'-AGTCAGCAGCCAGTCTCAG-3'
GAPDH	Sense: 5'-GGAGCGAGATCCCTCCAAAAT-3'
	Antisense: 5'-GGCTGTTGTCATACTTCTCATGG-3'

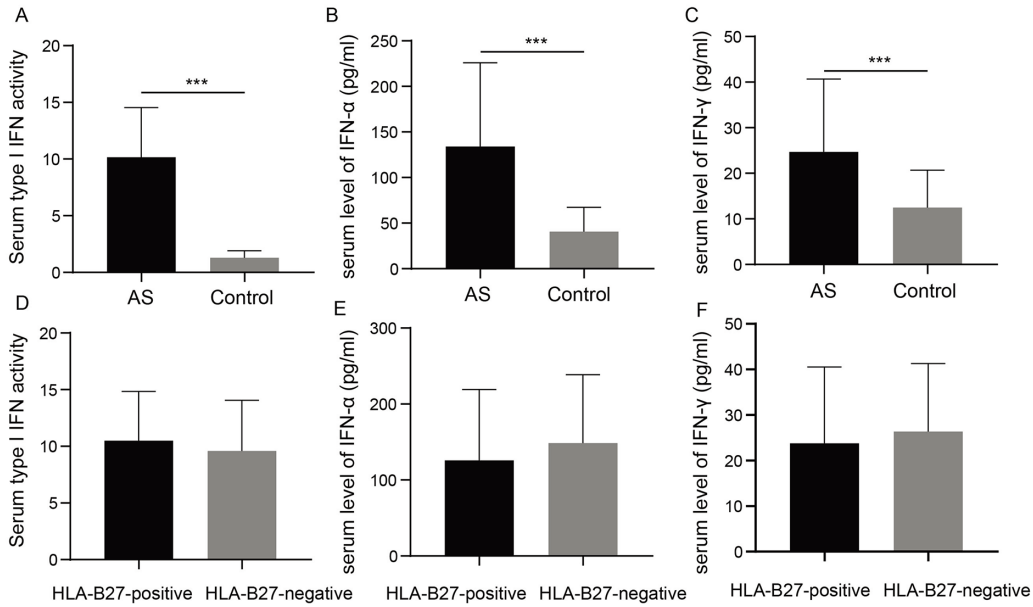

Fig. 1. Induction of type I and II IFN production in ankylosing spondylitis.
A. The serum type I IFN activity. The relative expressions of *MX1*, *PKR* and *IFIT1* in ankylosing spondylitis patient sera (n = 50) were determined by qPCR, normalized to those in healthy control sera (n = 50), and then summed to a score determining the ability of sera to induce IFN-induced gene expression, namely serum type I IFN activity. B. ELISA detection of serum concentration of IFN-α in ankylosing spondylitis patients (n = 50) and healthy controls (n = 50). C. ELISA detection of serum concentration of IFN-γ in ankylosing spondylitis patients (n = 50) and healthy controls (n = 50). D. The serum type I IFN activity between HLA-B27-positive patients (n = 32) and HLA-B27-negative patients (n = 18). E. The serum concentration of IFN-α between HLA-B27-positive patients (n = 32) and HLA-B27-negative patients (n = 18). F. The serum concentration of IFN-γ between HLA-B27-positive patients (n = 32) and HLA-B27-negative patients (n = 18). ***$p < 0.001$.

PGADA scores of ankylosing spondylitis patients (data not shown). These data suggest that induction of type I and II IFN production may contribute to ankylosing spondylitis progression.

Association between type I and II IFN production and pro-inflammatory factor production in ankylosing spondylitis

The Pearson correlation analysis also showed that the serum type I IFN activity was positively correlated with the production of CRP ($r = 0.590$, $p < 0.0001$), TNF-α ($r=0.711$, $p < 0.0001$), IL-1β ($r=0.585$, $p < 0.0001$), and IL-6 ($r = 0.727$, $p< 0.0001$) in ankylosing spondylitis patients (Fig. 3A). The serum level of IFN-α was positively correlated with the production of CRP ($r = 0.585$, $p < 0.0001$), TNF-α ($r=0.578$, $p< 0.0001$), IL-1β ($r= 0.491$, $p < 0.0001$), and IL-6 ($r =0.682$, $p< 0.0001$) in ankylosing spondylitis patients (Fig. 3B). The serum level of IFN-γ were positively correlated with the production of CRP ($r=0.531$, $p < 0.0001$), TNF-α ($r=0.564$, $p < 0.0001$), IL-1β ($r = 0.477$, $p < 0.0001$), and IL-6 ($r=0.509$, $p < 0.0001$) in ankylosing spondylitis patients (Fig. 3C). These data suggest that induction of type I and II IFN production may be associated with the release of pro-inflammatory factors in ankylosing spondylitis.

Type I and II IFN production in ankylosing spondylitis after anti-TNF treatment

The mean value of serum type I IFN activity were significantly decreased from 10.16 at baseline to 6.97, 4.62, 3.53, and 2.45 at the M1, M2, M4, and M6 after anti-TNF treatment ($p < 0.001$, Fig. 4A), and these decreases exhibited time-dependent manner ($p < 0.001$). The mean value of serum IFN-α level was remarkably reduced from 134.01 pg/ml at baseline to 95.19 pg/ml, 75.77 pg/ml, 62.73 pg/ml, and 50.07 pg/ml at the M1, M2, M4, and M6 after anti-TNF treatment ($p<0.001$, Fig. 4B), and these reductions exhibited time-dependent manner ($p < 0.01$). The serum level of IFN-γ level was notably declined from 24.69 pg/ml at baseline to 19.69 pg/ml, 16.89 pg/ml, 14.38 pg/ml, and 12.74 pg/ml at the M1, M2, M4, and M6 after anti-TNF treatment ($p< 0.001$, Fig. 4C), and these declines exhibited time-dependent manner ($p < 0.01$). These data suggest that anti-TNF treatment may inhibit the induction of type I and II IFN production in ankylosing spondylitis.

Association between type I and II IFN production and clinical response to anti-TNF treatment

The overall population was allowed to receive response evaluation by ASAS40 response after anti-TNF treatment. There were 9 (18.0%), 15 (30.0%), 22 (44.0%), and 29 (58.0%) ankylosing spondylitis patients reaching

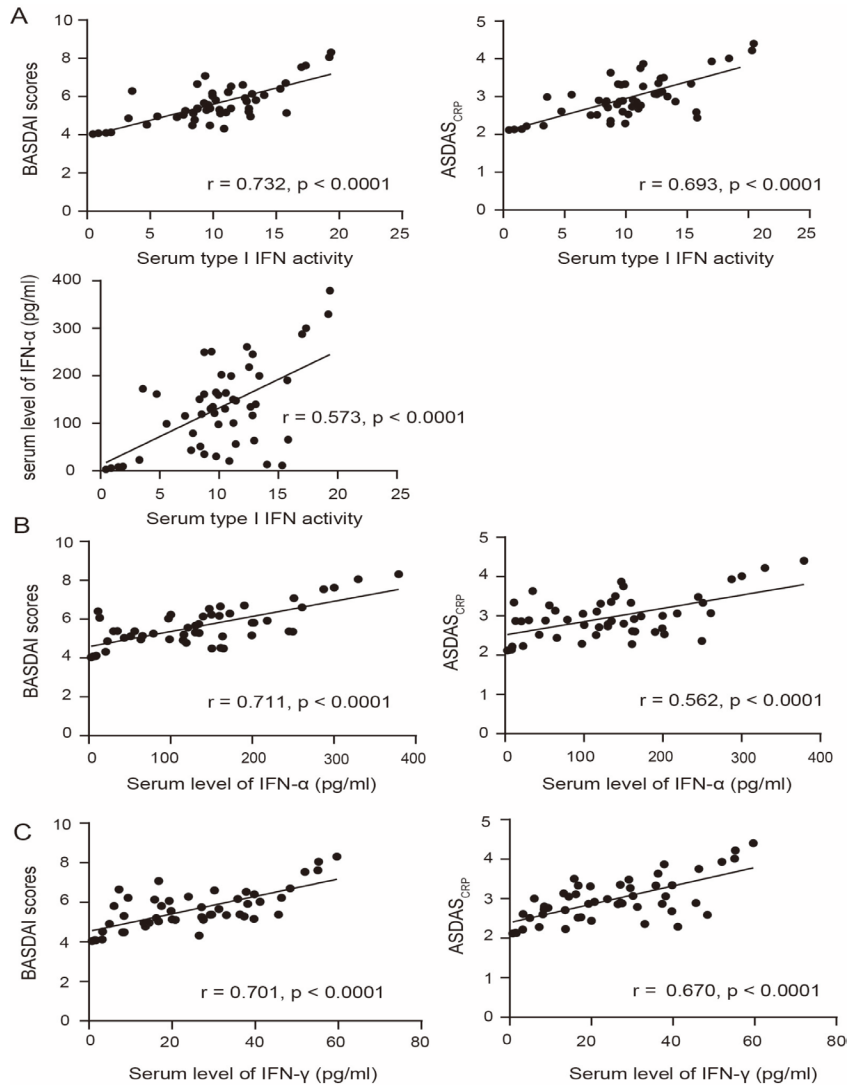

Fig. 2. Association between type I and II IFN production and disease activity in ankylosing spondylitis.
A. Pearson correlation analysis of serum type I IFN activity with BASDAI scores, $ASDAS_{CRP}$, and the serum level of IFN-*α* of ankylosing spondylitis patients. B. Pearson correlation analysis of serum concentration of IFN-*α* with BASDAI scores and $ASDAS_{CRP}$ of ankylosing spondylitis patients. C. Pearson correlation analysis of serum concentration of IFN-*γ* with BASDAI scores and $ASDAS_{CRP}$ of ankylosing spondylitis patients.

ASAS40 response at the M1, M2, M4, and M6, respectively. The responders (n = 29) were demonstrated with reduced serum type I IFN activity (Fig. 5A) concomitant with lower serum levels of IFN-*α* (Fig. 5B) and IFN-*γ* (Fig. 5C) compared to the non-responders (n = 21) from the baseline to the M1, M2, M4, and M6 after anti-TNF treatment ($p < 0.05$). The serum type I IFN activity, and the serum levels of IFN-*α* and IFN-*γ* were used as a test to predict responders and non-responders to anti-TNF treatment produced an AUC of 0.837 (Fig. 5D), 0.814 (Fig. 5E), and 0.787 (Fig. 5F), respectively. These data indicate that a reduced production of type I and II interferons may be associated with better treatment response for ankylosing spondylitis patients after anti-TNF treatment.

Discussion

Although a low disease activity along with inhibition of radiographic progression have been demonstrated in patients after use of anti-TNF biologic drugs, the failure to achieve desired treatment goals occurs in nearly 50% of patients who have an increased risk of clinical progression (Ornbjerg et al. 2019). Several common baseline parameters, such as young age, male sex, short disease duration, HLA-B27 genotype, and CRP level could be indicative of a better response to anti-TNF treatment among ankylosing spondylitis patients (Ornbjerg et al. 2022). However, more solid data in large patient cohorts are required for their application in the clinical practice. Actually, identifying ankylosing spondylitis patients with less response to anti-TNF treatment is as important as identifying responders. If

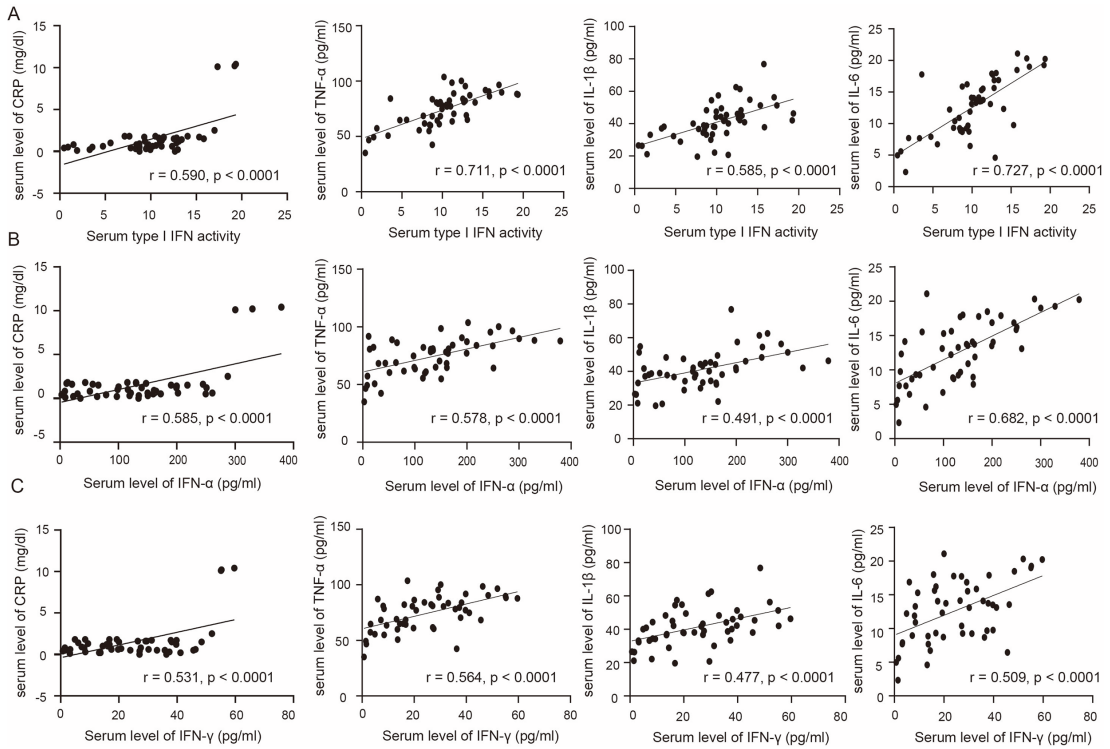

Fig. 3. Association between type I and II IFN production and pro-inflammatory factor production in ankylosing spondylitis. A. Pearson correlation analysis of serum type I IFN activity with serum levels of TNF-α, IL-1β, and IL-6 of ankylosing spondylitis patients. B. Pearson correlation analysis of serum concentration of IFN-α with serum levels of TNF-α, IL-1β, and IL-6 of ankylosing spondylitis patients. C. Pearson correlation analysis of serum concentration of IFN-γ with serum levels of TNF-α, IL-1β, and IL-6 of ankylosing spondylitis patients.

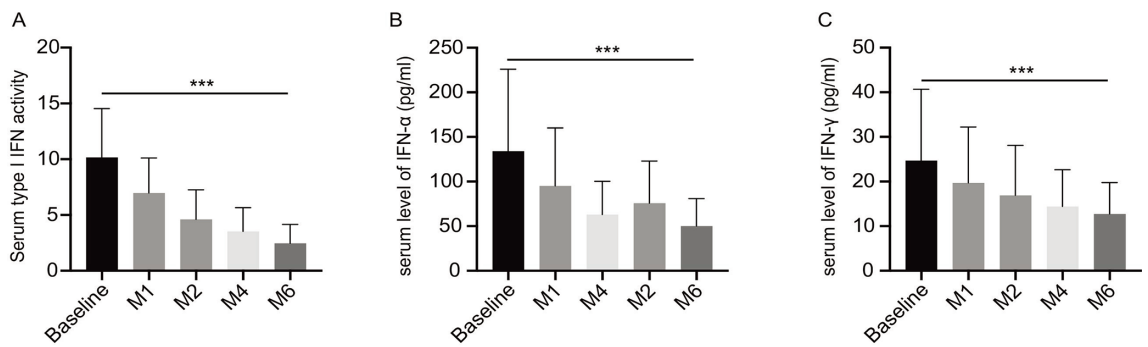

Fig. 4. The serum type I IFN activity (A), the serum levels of IFN-α (B) and IFN-γ (C) in ankylosing spondylitis patients (n = 50) after anti-TNF treatment.
***p < 0.001.

the patients were expected to receive low benefit from anti-TNF biologic drugs, further treatment decisions were made; only short trials of anti-TNF biologic drugs or to the switch to other biological agents, such as IL-17 inhibitors or instance JAK inhibitors. In this regard, we are intended to find more specific predictors for assessment of the short-term treatment response to anti-TNF biologic drugs in ankylosing spondylitis patients. We found that the more significant increase in blood type I and II IFN production correlated with poorer improvement of disease activity during the 6-month treatment in ankylosing spondylitis.

The action of type I IFNs includes the increase of immune response, more effective elimination of viral infection, and generation of memory responses against future viral challenge by exerting effects on myeloid cells, B cells, T cells and NK cells (Ivashkiv and Donlin 2014). Surprisingly, a number of patients have evidence of a high type I IFN signature in more active disease in their peripheral blood mononuclear cells among several autoantibody-associated autoimmune conditions including systemic lupus erythematosus (Postal et al. 2020), rheumatoid arthritis (Rodriguez-Carrio et al. 2015), systemic scle-

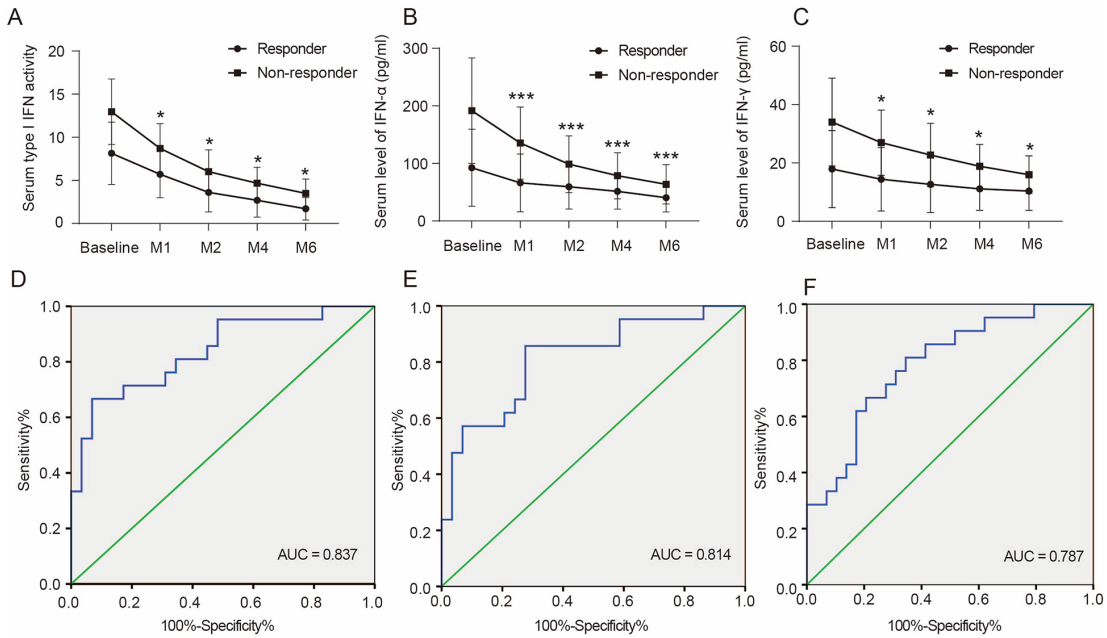

Fig. 5. The serum type I IFN activity and the serum levels of IFN-α and IFN-γ, and the ROC curves in responders and non-responders to anti-TNF treatment.
The serum type I IFN activity (A), the serum levels of IFN-α (B) and IFN-γ (C) in responders (reaching ASAS40 response; n = 29) and non-responders (without reaching ASAS40 response; n = 21) from the baseline to the M1, M2, M4, and M6 after anti-TNF treatment. The ROC curves with AUC were plotted to show the serum type I IFN activity (D), and the serum levels of IFN-α (E) and IFN-γ (F) used as a test to predict responders and non-responders to anti-TNF treatment. *p < 0.05, ***p < 0.001.

rosis (Skaug and Assassi 2020), dermatomyositis (Lu et al. 2017), Sjögren's syndrome (Nezos et al. 2015), and multiple sclerosis (Reder and Feng 2014). Two predominate factors of type I IFNs, IFN-α and IFN-β, are found to be harmful by uncontrolled inflammation leading to tissue damage that aggravate disease (Davidson et al. 2014). A link between sustained type I IFN activity and disease progression can be explained by the possibility that IFN-α and IFN-β induce pathogenic Th17 cell accumulation and thereby leading to high disease activity (Klasen et al. 2019). In addition, IFN-γ and IL-23/IL-17 cytokines play a dominant role in the inflammatory and proliferative cascades of ankylosing spondylitis (Raychaudhuri and Raychaudhuri 2016). High type I IFN activity and increased IFN-γ were both linked to distinct clinical features of active systemic lupus erythematosus (Oke et al. 2019). In line with other investigators, we found the serum type I IFN activity, and the serum levels of IFN-α and IFN-γ in a cohort of patients with ankylosing spondylitis at baseline were notably greater than the healthy controls in this study. The data presented here implied that the induction of type I and II IFN production is not just an epiphenomenon in ankylosing spondylitis, but might be a heritable risk factor.

Although the efficacy of TNFi for ankylosing spondylitis is well-recognized, the globally patterns of TNFi applying differs among countries in clinical practice, such as adalimumab frequently prescribed in Korea, Sweden, and Brazil (Lie et al. 2017; Acurcio et al. 2020; Lee et al. 2022a), whereas etanercept commonly used in the USA and Canada (Walsh et al. 2018). However, no evidence shows a particular TNFi drug with better efficacy than the others (Grubisic et al. 2022). This study retrospectively analyzed ankylosing spondylitis patients receiving adalimumab as TNFi. We validated the pilot data and analyzed the association between type I and II IFN production, the disease activity and treatment response to anti-TNF biologic drugs. A previous pilot study suggests a clear relationship between IFN-regulated gene expression and response to TNFi in ankylosing spondylitis (Harrison et al. 2021). A negative correlation between the type I IFN signature and the clinical response to rituximab treatment in rheumatoid arthritis patients was previously reported (Thurlings et al. 2010). Concurring with these earlier investigators, we presented a novel observation of a significant reduction in type I and II IFN production with low disease activity in ankylosing spondylitis patients receiving 6-month treatment of adalimumab and in those reaching ASAS40 response.

In conclusion, our findings extend previous knowledge that the induction of type I and II IFN production may be involved in the pathogenesis of ankylosing spondylitis and negatively predicts patient response to anti-TNF biologic drugs in ankylosing spondylitis. These observations not only extend the understanding of disease mechanisms and of individual tailoring of IFN-targeting therapies in ankylosing spondylitis, but also provide a potential factor to identify responders or non-responders to anti-TNF treat-

ment in ankylosing spondylitis that facilitates personalized decision-making in clinical practice. Large sample sizes in future investigations are needed to i) determine the serum levels of IFN-β and type III IFN family, especially IFN-λ1, in ankylosing spondylitis and ii) confirm to what degree a value contributes independently to the prediction of clinical response following 6-month treatment and to the prediction of long-term drug withdrawal.

Author Contributions

H.Y.L. conceived the study and wrote the first draft of manuscript. L.B. and J.Z.H. contributed to data collection, data analysis, and visualization. Y.C.C. completed manuscript revisions. All authors reviewed the manuscript.

Conflict of Interest

The authors declare no Conflict of Interest.

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