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Article

Ustekinumab treats psoriasis by suppressing RORC and T-box but its suppression of GATA restrains its efficacy

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Psoriasis is a T-cell mediated disease that involves IL-23/Th17 and IL-12/Th1 axes. Ustekinumab, a fully human monoclonal antibody targeting the p40 subunit of both IL-12 and IL-23, has proven to be efficient and safe for treating patients with psoriasis. Yet, there have been no reports with human skin/blood samples that would elucidate the molecular mechanisms by which ustekinumab calms psoriasis skin lesions. To investigate the efficacy and molecular pathway (RORC, t-BOX and GATA) of ustekinumab in treating patients with psoriasis skin lesions. A total of 30 patients with psoriasis were randomized into placebo group and treatment group. PASI of each patient was calculated at 0, 12 and 24 weeks post-treatment. The mRNA levels of RORC, t-BOX and GATA in peripheral blood mononuclear cells separated from patients' whole blood were analyzed using qPCR. Decreased mRNA of RORC, t-BOX and GATA were observed after continuous injections, indicating that ustekinumab exerts its effect by interacting with these molecules; while no significant difference in foxp3 mRNA levels were found between placebo group and treatment group.

Keywords: Psoriasis. Ustekinumab/efficacy. Biologic agents.

INTRODUCTION

Psoriasis is a chronic, inflammatory and proliferative skin disease, characterized by impaired differentiation, overactive hyperproliferation of epidermal keratinocytes, disturbed keratinization and aberrant activation of T lymphocytes. It involves complicated pro-inflammatory cytokine networks, where Th1/Th2 homeostasis, Th17/Treg balance, IL-23/Th17 axis and IL-12/Th1 axis have shown to have important roles (Deng, Chang, Lu, 2016; Harden, Krueger, Bowcock, 2015). IL-12 and IL-23 have shown to be involved in the development of Th1 and Th17 immune responses in psoriasis (Lee *et al.*, 2004; Yawalkar *et al.*, 2009), and thus have become potential targets for treating patients with psoriasis.

Ustekinumab, a new class of anti-cytokine drugs, is a human monoclonal antibody that targets the p40 subunit of both IL-12 and IL-23, and thus directly neutralizes their biological activity, and decreases the immune cell activation properties of IL-12 and IL-23. Several clinical trials have demonstrated the superior clinical efficacy and safety of ustekinumab in the treatment of moderate-to-severe psoriasis and psoriatic arthritis (Kavanaugh *et al.*, 2014; Nast *et al.*, 2015; Strober *et al.*, 2016; Tsai *et al.*, 2011) with sustained efficacy after 3 years of treatment (Kimball *et al.*, 2012). Nevertheless, according to PASI-75 (PASI: Psoriasis area-and-severity index) its efficiency was lower than in IL-17 pathway blockers, for example, secukinumab (Tan, Griffiths, 2016).

Ustekinumab stimulates peripheral blood monocytes (PBMC) so as to modulate cytokines (Nograles *et al.*, 2008; Reddy *et al.*, 2010). However, to our knowledge, there have been no reports with human skin/blood samples elucidating the pathway by which ustekinumab modulates full blood white cells thus influencing human keratinocytes' cellular processes. There are also no reports on how ustekinumab achieves its efficacy in the treatment of psoriasis and/or presents distinctive properties from other biologic agents.

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Retinoic acid-related orphan receptor γ (RORγ, the human form: RORC) is the key transcription factor involved in IL-17-producing cells (Zhang *et al.*, 2015). The inhibition of RORC has shown to be effective in decreasing psoriatic lesions (Rizvi, Chaudhari, Syed, 2015; Takaishi *et al.*, 2017). Furthermore, transcription factor forkhead box P3 (foxp3) is a marked factor of regulatory T cells (Treg) development (Williams, Rudensky, 2007) and its interaction with RORC can inhibit IL-17 (Ichiyama *et al.*, 2008). T-box family of transcription factors is a master determinant of Th1 lineage (Szabo *et al.*, 2000). GATA-3 encodes a protein belonging to the Th2-specific transcription factors, promoting Th2 differentiation (Lantelme *et al.*, 2001) and inducing Th2 cytokine production in an analogous way to T-box (Lee *et al.*, 2000). Dominance of Th1 over Th2 is related with psoriasis (Zhu *et al.*, 2010).

Our aim was to verify our assumption that ustekinumab has longer sustainment because it can interact with RORC, T-box, foxp3 and GATA. The real-time qPCR was carried out to detect the changes it caused on mRNA levels in patients treated with placebo (P group) and ustekinumab-treated patients (U group).

MATERIAL AND METHODS

Patients, inclusion and exclusion criteria

Patients with psoriasis were enrolled in the 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China. The period of the study was 30 months.

The inclusion criteria were the following: (1) patients with moderate to severe plaque psoriasis; (2) patients between 18-65 years old, diagnosed with plaque psoriasis for at least 6 months before the beginning of the study; (3) patients with PASI > 12, and skin lesion area takes up > 10% of total body surface area; (4) patients with no history of biologic agents treatment.

Exclusion standards were: (1) patients with erythrodermic psoriasis or psoriatic arthritis or psoriasis pustulosa or psoriasis guttate; (2) patients with severe and uncontrollable local or systematic acute/chronic infections; (3) patients with active or potential tuberculosis or asthma; (4) patients with malignancy history; (5) patients with other severe systematic disease; (6) patients who were prescribed with drugs or biologic agent; (7) patients who received immunosuppressor within 1 month or (8) psoriasis systematic treatment or phototherapy within 1 month or (9) psoriasis topical agents within 2 weeks.

The study was approved by the Medical Ethics Committee of the 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China (approval number is 2009-32).

Treatment

Patients were treated with ustekinumab according to previously described approach (Tsai, Ho, 2011). In the present study, we designed a crossover tests based on the ethics (Figure 1). Patient in the treatment group (U group) were subcutaneously injected with 45 mg ustekinumab at weeks 0, 4, 16, and 0.9% NaCl at week 12; while the placebo group (P group) was subcutaneously injected with 0.9% NaCl at weeks 0 and 4, and 45 mg ustekinumab at weeks 12 and 16.

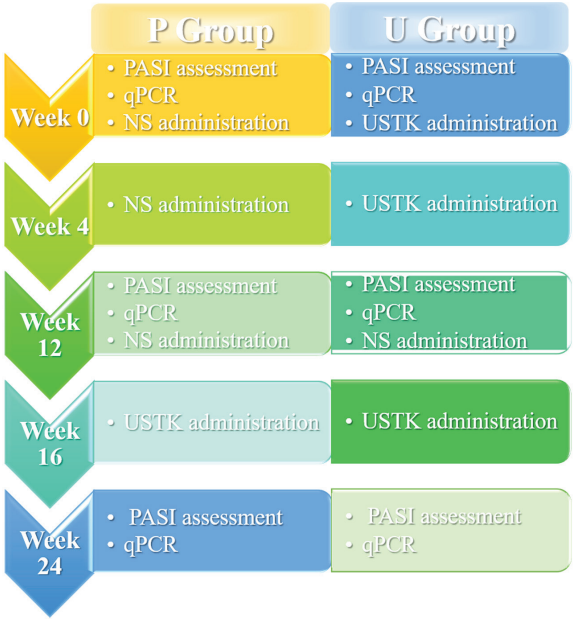

FIGURE 1 - Flowchart of the study. USTK: Ustekinumab. P Group: placebo group. U Group: Ustekinumab group.

Efficacy assessment

PASI was adopted for the efficacy assessment; when PASI improvement rate reached or exceeded 75% (PASI-75), the treatment was considered effective. PASI of each patient was calculated at weeks 0, 12 and 24, respectively; in weeks 0 and 12, PASI was measured before administration of NaCl or ustekinumab.

Sample collection

Whole blood samples were collected at weeks 0, 12 and 24 post- treatment.

Whole blood red blood cell lysis buffer preparation

10x stock solution was prepared consisting of 89.9 g NH_4Cl, 10.0 g $KHCO_3$, 370.0 mg tetrasodium EDTA, following pH adjustment to 7.3. The solution was then dissolved in 1 liter of pure water.

RNA extraction and real-time quantitive PCR

Red blood cells in whole blood samples were dissolved by whole blood red blood cell lysis buffer. Then total RNA was isolated from patients' peripheral leukocytes using invitrogen™ Trizol™. cDNA was prepared using Superscript II Reverse Transcriptase (Invitrogen). Gene expression was determined using SYBR green PCR mix (Roche) and 10 ng template. Real-time PCR analysis was performed using ABI StepOne Plus instrument under the following amplification conditions: 5 s at 95 °C, followed by 45 cycles of 30 s at 60 °C (RORC); 5 s at 95 °C, followed by 45 cycles of 30 s at 60 °C (FOXP3); 5 s at 95 °C, followed by 45 cycles of 30 s at 60 °C (T-box21); 5 s at 95 °C, followed by 45 cycles of 30 s at 60 °C (GATA). Primers for RORC (5'-CAATGGAAGTGGTGCTGGTTAG-3', 5'-GGGAGTGGGAGAAGTCAAAGAT-3'), FOXP3 (5'-ATTCCCAGAGTTCCTCCACAAC-3', 5'-ATTGAGTGTCCGCTGCTTCT-3'), T-box (5'-GCCCCTTCTCCTTTTGATAA-3', 5'-CGGTGTCCTCCAACCTAATAAC-3') and GATA (5'-AGACCACCACAACCACACTCT-3', 5'-GATGCCTTCCTTCTTCATAGTCA-3') were designed using Beacon designer (Premier Software). Transcript expression was normalized to the GAPDH house-keeping gene and represented as either $2^{-\Delta\Delta C}{}_T$ ($2^{-\Delta\Delta C}{}_T$=$2^{-\Delta C}{}_T$ (gene of interest/average [$2^{-\Delta C}{}_T$ (house-keeping gene)]) in the case of p35 or p40 expression.

Statistics and graph making

Differences between every two groups were evaluated with unpaired two-tail *t*-test. PASI75 rates (percentages of PASI improvement rate reaching or exceeding 75% of P and U groups, PASI75%) were compared between P and U groups using kappa test. PASI improvement rate (W12vsW0 or W24vsW0)=[PASI(Week0)-PASI(Week12 or Week24)]/PASI(Week0). *p<0.05, **p<0.005, ***p<0.0001. Data analysis and graphs were performed using Prism software (GraphPad software, Inc.). In all the graphs, ● stands for P group, and ▲ stands for U group.

RESULTS

A total of 30 patients with psoriasis were enrolled (age: 18-60 years old; 7 females and 23 males). Initial PASI ranged from 12.2 to 55.6. The average PASI was 22.86. The standard error of mean (SEM) of PASI was 1.96. Patients were double-blindly and randomly divided into placebo group (P group, n=16, average PASI=23.06, SEM of PASI=3.40) and ustekinumab-treated group (U group, n=14, average PASI=22.64, SEM of PASI=1.80). One patient did not sign the informal consent for the mRNA level test, therefore his mRNA data were excluded from the study.

Maximum drug efficacy can be obtained within 2 injections of ustekinumab

To demonstrate the clinical efficacy of ustekinumab, we investigated the intergroup and intragroup comparisons of individual's PASI at 3 different time-points (Figure 2). Briefly, a significant decrease in PASI was observed in U group at week 12 compared to P group. In addition, in the U group, PASI decreased significantly at weeks 12 and 24, compared to week 0; nevertheless, no significant difference was found between weeks 12 and 24. Besides, in the P group, PASI decreased significantly at week 24 compared to week 0.

With the reference to PASI-75 rate, higher PASI-75 rate was found in the U group compared to P group, and

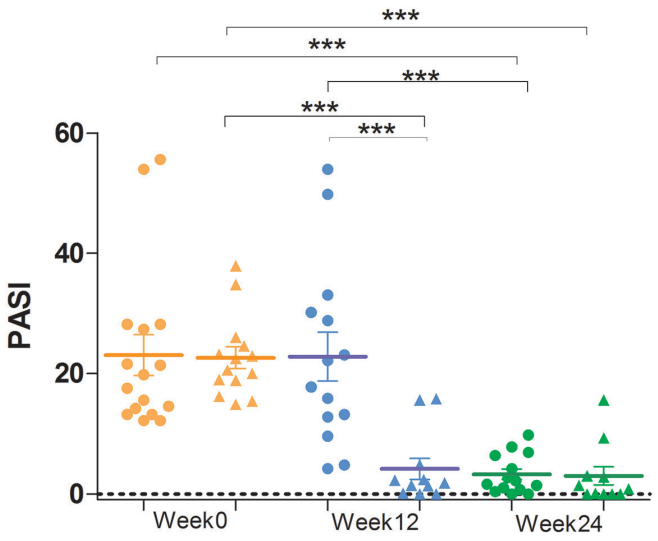

FIGURE 2 - Intragroup and intergroup comparisons of PASI in different timepoints. There are highly significant differences between P group and U group at Week 12. There are significant differences in P group between week 0 and week 24, in U group between weeks 0 and 12, 24 respectively. ● stands for P group, and ▲ stands for U group.

TABLE I - Kappa tests of PASI of P group and U group, comparing week 12 to week 0, week 24 to week 0 respectively

	W12 vs. W0		W24 vs. W0	
	PASI-75 (n)	PASI improvement rate≤75% (n)	PASI-75 (n)	PASI improvement rate≤75% (n)
P group	2	14	13	3
U group	10	4	12	2
P value	–	0.001**	–	0.74

this was also verified by kappa test (Table I); significant differences were found at week 12 compared to week 0 (p=0.001013), while no significance was detected between week 24 and week 0 (p=0.74), indicating no significant improvement in PASI-75 rate at week 24.

To sum up, the results indicated that ustekinumab is effective in treating psoriasis skin lesions; ustekinumab can reach the maximum efficiency after 2 injections, and then its treatment effect remains constant overtime.

Multiple injections of ustekinumab suppresses RORC, t-BOX, GATA but not foxp3 mRNA

With reference to RORC mRNA, a significant difference between week 0 and week 24 was found in group U (**Figure 3a**), while in P group there were no significant differences at different time-points, and between U group and P group. Furthermore, a significant difference in t-BOX and GATA mRNA levels between

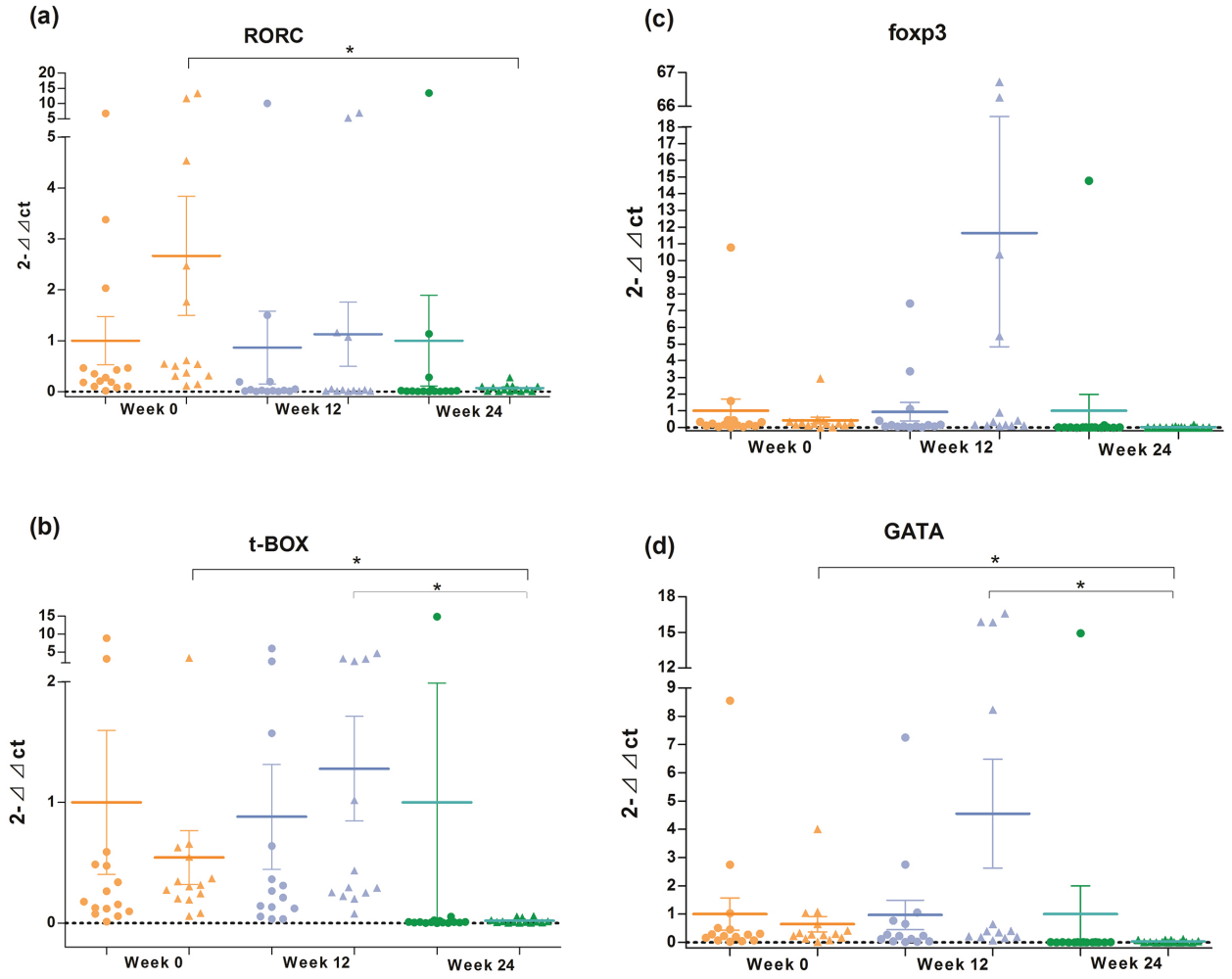

FIGURE 3 - Intergroup and intragroup comparisons of RORC **(a)**, t-BOX **(b)**, foxp3 **(c)** and GATA **(d)** mRNA levels at weeks 0, 12 and 24. ● stands for P group, and ▲ stands for U group.

week 24 and weeks 0 or 12 were found in group U (**Figure 3b** and **3d,** respectively). Hence, this raises a question if the expressions of GATA and t-BOX are parallel one to another. In addition, no significant difference in foxp3 mRNA levels were found between groups (Figure 3c).

To sum up, our data suggested that ustekinumab suppresses RORC, t-BOX and GATA. In addition, the maximum suppression effect of RORC can be achieved after 3 injections, while the maximum suppression effect of both t-BOX and GATA can be achieved after 2 injections. Also, it seems that ustekinumab has no effect on foxp3 expression.

DISCUSSION

Great progress has been made in declaring different roles of different T cell subsets. Among these cell types, T helper 17 (Th17) and other IL-17–producing cells, notably γδ T cells and CD8+ T cells, have been in the center of attention. IL-23/Th17 axis mainly controls the proinflammatory loop in psoriatic plaques (Diani, Altomare, Reali, 2016; Kryczek *et al.*, 2008). Based on our PASI assessment, there were significant differences between P group and U group at week 12 post-treatment. There were significant differences in P group between weeks 0 and 24, in U group between weeks 0, 12, and 24 respectively. These results indicated that two injections of ustekinumab were sufficient for maximal efficacy. According to the instructions, in case of moderate to severe plaque psoriasis and active psoriatic arthritis, the recommended dose of ustekinumab is 45 mg administered at week(s) 0 and 4, and then every 12 weeks. Therefore, we hypothesized that the third and following injections might intensify ustekinumab's effect or prolong its efficacy.

RORC is the key transcription factor involved in the production and regulation of IL-17 from Th17, γδT cells, innate lymphoid (ILCs), lymphoid tissue inducer (LTi) cells (Fauber, Magnuson, 2014; Isono, Fujita-Sato, Ito, 2014; Yang *et al.*, 2014; Zhang, Luo, 2015) and IL-22 and IL-23 from Th17 (Smith *et al.*, 2016). Various antibodies, both upstream and downstream of RORC, specifically anti-IL-12p40 and anti-IL-17A agents have shown to be efficacious in the treatment of psoriasis (Rizvi, Chaudhari, 2015). Takaishi *et al.* (2017) have described attenuation of psoriasis-like lesions in two independent psoriasis mouse models after oral administration of RORγt (a specific transcript of the RORC gene) antagonist and suggested that this effect was based on neutralization of IL-17-producing cells. Our data showed that ustekinumab has an RORC-suppressing effect during long-term use, which is helpful in improving psoriatic skin lesions, and probably associated with its anti-IL12/23 effect.

Foxp3 is one of the most specific markers used to identify Regulatory T Cell (Tregs). Overexpression of Foxp3 is required to maintain function and lineage identity of mature peripheral Tregs (Williams and Rudensky, 2007). Upregulated Foxp3 initially binds to RORγt, thereby reducing IL-17A expression and inhibiting RORγt-mediated IL-17A promoter activity (Ichiyama, Yoshida, 2008). Etanercept, a TNF inhibitor, can induce transcriptional levels of Foxp3, STAT3 and STAT4 mRNA in responding patients with psoriasis (Quaglino *et al.*, 2011). Adalimumab, also a TNF-inhibiting medication expands functional Foxp3+ Tregs via binding monocyte membrane TNF (Nguyen *et al.*, 2016). Accordingly, foxp3 is upregulated by the neutralization of TNF. Our results indicated that ustekinumab didn't suppress or enhance foxp3 mRNA levels, at least not within 3 injections. Probably, ustekinumab decreases psoriatic skin lesions independently from TNF pathway. On the other hand, it can be used as a substitute for anti-TNF agents in patients not responding to anti-TNF agents, since psoriasis has multiple pathogenic mechanisms.

As the upstream of the IL-17 drives the proinflammatory loop, Th1 produces interferon-γ (IFN-γ) favoring the recruitment and expansion of IL-17-producing cells (Diani, Altomare, 2016; Kryczek, Bruce, 2008). T-box family of transcription factors is a main determinant of Th1 lineage (Szabo, Kim, 2000). Memory CD4+ T cells express a high level of T-box. Pre-mobilization of T-box into nuclei might have more important roles at early time points for rapid responses of memory T cells (Yu *et al.*, 2014). Expression of the human T-box correlates with IFN-γ expression in Th1 and natural killer cells (Yu, Zhang, 2014), suggesting that this gene is initiating Th1 lineage development from naive Th precursor cells. T-box sustains the effector function of CD8+ T cells through regulation of CD8+ T cell proliferation, suppressed expression of inhibitory receptors such as PD-1, and promotion of IFN-γ and perforin secretion (Lazarevic, Glimcher, 2011). Our data demonstrated that ustekinumab can inhibit T-box expression. Combining current discoveries, it needs further investigation whether ustekinumab can affect nuclei-located T-box.

GATA-3 encodes a protein that belongs to the Th2-specific transcription factors, promoting Th2 differentiation (Lantelme *et al*., 2001) and inducing Th2 cytokine production in an analogous way to T-box (Lee, Takemoto, 2000). Regulation of Th1/Th2 balance can be mediated by the level of T-box and GATA-3 (Park *et al.*, 2009). The expression of GATA is, however, markedly

up-regulated in cells differentiating along the Th2 lineage, and is down-regulated in cells differentiating along the Th1 pathway (Frisullo *et al.*, 2006). Compared to healthy controls, a significantly higher expression of T-box mRNA and lower expression of GATA-3 mRNA were tested in PBMCs of psoriatic patients, and consequently, a much higher T-box/GATA-3 ratio was found in patients than in controls (Zhu *et al.*, 2010). The high T-box and low GATA-3 expression in PBMCs and lesioned skin of psoriatic patients indicates a skew towards the Th1 pathway of T-helper cell activation. T-box and GATA-3 might be regulator genes in psoriasis via the Th1/Th2 balance. Furthermore, our data showed that ustekinumab suppressed GATA expression. From this perspective, it antagonizes the treatment of psoriasis.

To sum up, from the aspect of molecular mechanism, ustekinumab can be seen as a double-edged sword in psoriasis treatment. On the positive side, it suppresses the expression of RORC and T-box. On the negative side, it suppresses the expression of GATA and has no impact on foxp3. The effectiveness of Ustekinumab independent of TNF pathway reveals its potential effect for patients not responding to anti-TNF agents. Screening out patients responding to ustekinumab is the key to making best of the equilibrium between positive and negative sides and to obtaining the most ideal treatment outcome. Future randomized clinical trials are necessary to verify these findings.

DISCLOSURE

The authors declare that they have no conflicts of interest.

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