Infliximab-Induced Psoriasis and Psoriasiform Skin Lesions in Pediatric Crohn Disease and a Potential Association With IL-23 Receptor Polymorphisms

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ABSTRACT

Background: Infliximab (IFX), an established therapy for pediatric Crohn disease (CD), is also efficacious in treating psoriasis, a skin disorder, in which tumor necrosis factor-α is implicated pathogenically. Paradoxically, there have been numerous reports of new-onset psoriasis following tumor necrosis factor-α antagonist therapy in adult patients with inflammatory bowel disease, but pediatric data are sparse.

Methods: A retrospective review of all IFX-treated patients with CD, who subsequently developed psoriasis, at a single pediatric inflammatory bowel disease center, was performed. A subset of affected patients (10/18) and CD controls (147 of 172) treated with IFX but without the development of psoriasis were genotyped for polymorphisms in the interleukin-23 receptor (*IL-23R*) gene, which has been identified as conferring susceptibility to both CD and psoriasis.

Results: Eighteen (10.5%) of 172 IFX-treated patients with CD developed new-onset psoriasis (n = 17) or worsening of existing psoriasis (n = 1). The duration of IFX exposure was variable, ranging from 1 to 25 infusions. Three patients discontinued IFX because of this complication. Most patients responded well to topical steroid therapy. In comparison to disease-matched controls, patients with CD developing psoriasis following IFX therapy were more likely to be homozygous for specific polymorphisms in the *IL-23R* gene (rs10489628, rs10789229, and rs1343151).

Conclusions: As in adults, the development of psoriasis or psoriasiform skin lesions occurs in pediatric patients with CD treated with IFX. Adequately powered studies are required to further explore the preliminary findings reported here to determine whether polymorphisms in the *IL-23R* gene have a role in the pathogenesis of this paradoxical process, which presently remains unexplained.

Key Words: adverse events, Crohn disease, infliximab, psoriasis

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Biologic therapy with antibodies directed at tumor necrosis factor-alpha (TNF-α) constitutes a significant advance in the treatment of pediatric Crohn disease (CD), with efficacy demonstrated in the setting of chronically active intestinal inflammation despite immunomodulator therapy (1). Our group has previously reported restoration of normal growth during infliximab (IFX) therapy in children with such otherwise refractory CD (2). In addition to its now established role in the management of inflammatory bowel disease (IBD), TNF-α antagonists are used in treatment regimens for other inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis (3–9).

An unwanted effect associated with anti-TNF-α therapy in patients with CD has been the development of psoriatic skin lesions, which is surprising in view of the efficacy of IFX in the treatment of psoriasis. Numerous case reports, case series, and reviews have been published, mainly describing new-onset or worsening of existing psoriasis and psoriasiform exanthemata in adult patients following TNF-α antagonist therapy (10–14). To date, reported cases of new-onset psoriasis following IFX therapy in pediatric patients with IBD have been limited to case reports or small case series (15–20).

For many years, researchers have recognized an association between IBD (particularly CD, and to a lesser extent UC) and psoriasis, with an increased prevalence of psoriasis in patients with IBD and vice versa (21–23). These data suggest that genetic variants common to both conditions may exist (24). With the advent of genome-wide association studies, an increasing number of susceptibility genes have been identified for psoriasis (25–27), CD (28), and ulcerative colitis (UC) (29), making it possible to search for genetic polymorphisms common to these conditions. The interleukin-23 receptor (*IL-23R*) gene was identified as a CD

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susceptibility gene in a genome-wide association study of North American patients in 2006 (30). Polymorphisms in this gene have also been described in association with psoriasis. Similar to CD, both protective and risk alleles have been identified (25,31–33). The role of the IL-23 axis in the development of psoriasis in IFX-treated patients with IBD has not been explored.

The objective of the present study was to present our single-center experience of psoriatic skin lesions in pediatric patients with IBD and to investigate the role of polymorphisms within the *IL-23R* gene in the pathogenesis of this paradoxical process. To date this is the largest series of IFX-induced psoriasis and psoriasiform exanthemata in a pediatric IBD population.

METHODS

Patient Population

All children with IBD treated with IFX at The Hospital for Sick Children, Toronto, were identified by reviewing the SickKids IBD database. The medical records were reviewed to identify all those who developed psoriasis or psoriasiform lesions while receiving IFX therapy. It is our clinical practice to refer all patients with a suspected diagnosis of psoriasis to a pediatric dermatologist. Data pertaining to age at IBD diagnosis, indication for IFX, age at IFX initiation, duration of IFX exposure at the time of onset of psoriasis, use of concomitant medication, family or personal history of psoriasis, description of the skin eruption, treatment, and outcome were extracted. Data pertaining to nonpsoriasiform rashes were not extracted.

DNA Analysis

All children of white descent, recruited from The Hospital for Sick Children for genetic studies related to IBD in whom both IFX exposure status and the presence/absence of psoriasis was known, were eligible for this study's genetic subanalysis. Subjects were first classified by disease type (CD vs UC), and then subjects with CD were further subclassified by IFX exposure ± the development of psoriasis.

Genotyping and SNP Selection

Genotyping was performed using the Illumina genotyping system at the Center for Applied Genomics at The Children's Hospital of Philadelphia as part of a multicenter genome-wide association study conducted exclusively in patients with pediatric-onset IBD (34). This dataset included 19 single nucleotide polymorphisms (SNPs) that spanned the *IL-23R* gene. All SNPs within this dataset that had a reported association to either psoriasis or CD were retained. Eight of 19 SNPs were discarded because of minor allele frequencies <5%, and 6 because of being highly correlated with other SNPs within the dataset ($r^2 > 0.8$). A total of 5 SNPs were suitable for further analysis: rs2201841, rs10489628, rs10789229, rs1120026, and rs1343151.

Statistical Analysis

Descriptive statistics were used to describe patient clinical characteristics. Continuous variables were presented as medians with interquartile ranges. Categorical variables (IL-23R polymorphisms) were explored with χ^2 statistics and logistic regression. A variety of analyses were conducted to explore the relation between variation in coding sequences for the *IL-23R* gene and the development of psoriasis in IFX-treated patients with CD. Each analysis contrasted the frequency of the homozygous genotype. Comparisons were made between CD and UC; IFX-exposed versus nonexposed (subjects with CD only); and subjects with/without psoriasis (in IFX-exposed subjects with CD only). Frequencies were presented as percentages and summarized as an odds ratio where appropriate. Findings were considered statistically significant when the P value was <0.05. The study protocol was approved by the research ethics board of The Hospital for Sick Children.

RESULTS

Patients

Since its first availability in Canada via compassionate release to pediatric patients with CD in the year 2000 until March 2010, a total of 172 children and adolescents with CD in The Hospital for Sick Children IBD program have been treated with IFX using an induction regimen (infusions at 0, 2, and 6 weeks) followed by regularly scheduled maintenance infusions. Of these, 18 (10.5%) patients have developed psoriatic or psoriasiform skin lesions of varying severity while receiving IFX therapy. Features were consistent with plaque psoriasis in the majority of patients. Clinical characteristics of the individual patients are summarized in Table 1. Typical skin lesions are depicted in Figures 1 and 2. Psoriasis diagnoses were confirmed clinically by a pediatric dermatologist.

As summarized in Table 2, of the 18 pediatric patients experiencing new-onset psoriasis (n = 17) or worsening of pre-existing tendencies (n = 1), 12 (67%) were boys, in keeping with the male preponderance observed in pediatric CD patient populations. All patients were non-Jewish whites. Family history was positive for psoriasis in 3 patients, including both patients whose skin lesions were poorly responsive to topical therapies. Additionally, 2 brothers in the cohort (patients 12 and 13) developed psoriasis following IFX use, but had no other known family history. The number of IFX infusions received before the onset of psoriasis was variable. Eight patients (44.4%) were receiving concomitant immunomodulation at the time of onset of the skin lesions. No other potential precipitating causes for the psoriasis/psoriasiform skin lesions were identified in any patient, including major life stressors, recent trauma, or recent introduction of another medication.

Psoriasis was managed successfully with topical steroid treatment in 15 of 18 (83.3%) patients. Two patients (numbers 1 and 14) had more severe skin lesions. Patient 1, treated for severe perianal fistulizing and coexistent luminal inflammatory disease with combination IFX and azathioprine maintenance therapy, abruptly lost response related to formation of IFX antibodies. His chronic psoriasis resolved off IFX with initiation of oral prednisone. Patient number 14 developed particularly severe scalp psoriasis leading to hair loss despite topical treatments, as well as psoriasis of the palms and soles. The severity of her psoriasis necessitated discontinuation of anti-TNF therapy despite an otherwise beneficial effect. Patient number 2 refused chronic topical steroid treatment and requested discontinuation of IFX because of psoriasis on the dorsum of the hands. Lesions disappeared but recurred 18 months later, when IFX was reintroduced as treatment for his chronically active CD.

IL-23R Polymorphism Analysis

DNA was available on 234 subjects with IBD (147 with CD, 87 with UC). Treatment with IFX was initiated in 35 of 147 (23.8%) patients with CD. Psoriasis developed in 10 of 35 IFX-exposed patients with CD. There was no association between any of the interrogated SNPs and IFX exposure status (data not shown); however, 3 of the 5 polymorphisms tested (rs10489628, rs10789229, and rs1343151) were significantly more prevalent

TABLE 1. Clinical characteristics of patients developing psoriasis or psoriasiform lesions while receiving IFX

Patient	Sex/age at onset of CD, y	Age at IFX initiation, y	IFX exposure at psoriasis onset, y	No. IFX infusions received at psoriasis onset	Concomitant IM use at onset of psoriasis*	Known family/ Personal history of psoriasis	Description of skin lesion (location)	Treatment	IFX continued?	Outcome of psoriasis
1	M/13.2	13.2	1.0	9	AZA	Maternal grandmother	Erythematous scaly plaques (scalp and ears, abdomen, axilla)	TS and 10% SA, oral prednisone	No—discontinued because of loss of response (HACA positive)	Psoriasis resolved off IFX, has not recurred with ADA (commenced for active GI disease)
2	M/10.5	12.7	1.6	13	MTX	No	Erythematous plaques (dorsum of hands)	TS, discontinued anti-TNF	No	Psoriasis recurred once IFX recommenced
3	F/11	13.9	1.0	9	AZA	No	Erythematous scaly plaques (back and scalp)	TS	Yes	Resolved with TS. Now has episodic exacerbations
4	F/4.7	11.4	1.6	13	AZA	Maternal grandfather	Guttate lesions, scaly plaques (legs, labia majora, trunk)	TS	Yes	Resolved
5	M/9.5	12.1	2.4	17	No	Father	Scaly, erythematous plaques (posterior auricular region and buttocks	TS	Yes	Improved
6	F/9.9	10.2	2.9	21	No	No	Scaly plaques, some papules (scalp [main site], trunk [papules])	TS and SA	No	Intermittent flares requiring topical steroid treatment
7	M/11.6	13.1	2.1	16	No	No	Scaly, erythematous plaques (posterior auricular region)	TS	Yes	Resolved
8	M/6.9	14.3	0.3	4	6-MP	No	Scaly erythematous plaques (posterior auricular region and intertriginous areas [feet])	TS	Yes	Intermittent exacerbations, responds to TS
9	F/12.1	14.7	0.1	1	AZA	No	Scaly erythematous plaques (scalp)	TS and salicylic acid	Yes	Subsequently developed guttate psoriasis, treated topically
10	M/7.6	12.1	0.6	6	No	No	Scaly erythematous plaques (palmar and plantar surfaces, scalp)	TS	Yes	Resolved
11	M/13.5	16.4	0.7	7	AZA	No	Impetiginised guttate psoriasis, erythematous crusty lesions (forehead, scalp, upper arms, chest, upper legs, face)	TS	Yes	Resolved
12	M/12.7	15.8	0.3	4	No	Brother (case 13)	Erythematous scaly plaques (scalp)	TS	Yes	Improved, intermittent exacerbations
13	M/11.8	14.6	3.5	25	No	Brother (case 12)	Erythematous scaly plaques (scalp)	TS	Yes	Resolved
14	F/10.5	12.5	0.6	5	No	Great aunt	Erythematous scaly plaques (scalp, palmar, and plantar surfaces)	TS	No	Persistent psoriatic lesions necessitating IFX discontinuing
15	F/12.1	15.6	1.9	15	No	Grandfather, uncle	Erythematous scaly plaques (scalp)	TS and salicylic acid	Yes	Frequent flares, respond to topical therapy
16	M/6.1	10.1	2.3	21	MTX PO 7.5 mg weekly	No	Erythematous scaly plaques (adjacent to ileostomy site)	Stopped IFX	No (CD quiescent postcolectomy)	Awaited
17	M/14.9	16.9	0.5	5	No	No	Erythematous scaly plaques (foot, posterior auricular region)	TS	Yes	Resolved

TABLE 1. *Continued*

18	M/12.9	11	N/A (predates CD diagnosis	N/A	No	Personal history—psoriasis worsened with IFX therapy	Erythematous scaly plaques (trunk and scalp)	TS	Yes	Improved

6-MP = 6-mercaptopurine; ADA = adalimumab; AZA = azathioprine; CD = Crohn disease; GI = gastrointestinal; HACA = human anti-chimeric antibody; IFX = infliximab; MTX = methotrexate; SA = salicylic acid; TNF = tumor necrosis factor; TS = topical steroid.

* Before June 2006, our practice was to administer a concomitant immunomodulator in an attempt to reduce the risk of loss of response, presumed secondary to antibody formation. Following June 2006, our practice changed and infliximab was given as monotherapy.

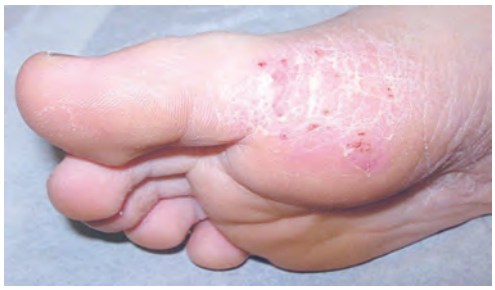

FIGURE 1. Scaly erythematous plaque at base of toe (patient no. 10).

among patients developing psoriasis following IFX therapy in comparison with patients with CD treated with IFX, but who did not develop psoriasis. Of note, despite similar allele frequencies, only 1 of these 3 polymorphisms (rs10489628) was able to clearly distinguish subjects with CD from subjects with UC. The effects demonstrated were independent in an additive fashion, with the simultaneous homozygous carriage of both rs10489628 and rs10789229 having the highest risk of IFX-induced psoriasis (odds ratio 17.5, $P = 0.02$, 95% CI 1.6–196.3). Interestingly, neither of the variants previously recognized to have an independent association with psoriasis de novo (rs2201841 and rs11209026) demonstrated any association with IFX-induced psoriasis. More important, we were unable to demonstrate an association between SNP rs11209026 (R381Q), the IL-23R SNP that has the strongest independent association with both CD and psoriasis susceptibility, and the development of IFX-induced psoriasis; all (35/35) subjects were homozygous for the common (G) allele of rs11209026. Numerically, more patients with UC than CD carried the protective ''A'' allele for this SNP (6% vs 1.5%, NS). Results of IL-23R SNP analyses are summarized in Table 3.

DISCUSSION

Psoriasis is a chronic skin disorder affecting approximately 2% of the population. Family history is often positive in affected patients (35,36). Psoriasis, either new-onset or worsening of existing lesions, has been described in association with all presently licensed TNF-α antagonists: IFX, adalimumab, etanercept, and

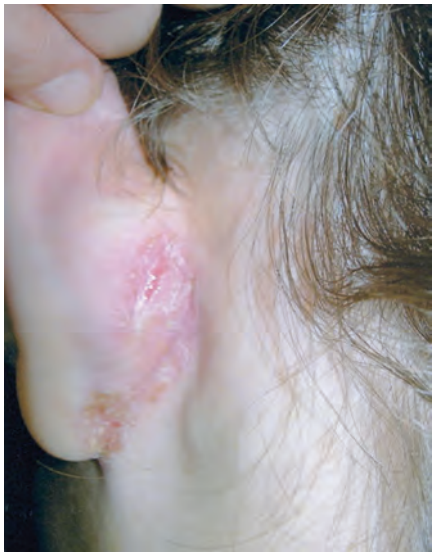

FIGURE 2. Erythematous lesion behind ear, with surface scaling and exudates (patient no. 5).

TABLE 2. Summary of the clinical characteristics of the patient group

Age at Crohn disease diagnosis (median and IQR)	11.3 y (IQR 9.5–12.7)
Age at onset of psoriatic skin lesions (median and IQR)	14.6 y (IQR 13.1–15.7)
Indication for infliximab	Persistent inflammatory luminal disease, despite immumomodulatory therapy, n = 13 Persistent inflammatory luminal disease, despite immumomodulatory therapy plus perianal disease, n = 1 Steroid-dependent inflammatory luminal disease (including upper GI tract involvement) and poor growth, n = 1 Perianal disease, n = 3
Duration of infliximab exposure at psoriasis onset (median and IQR)	1.0 y (IQR 0.6–2.1)
Median infliximab dose and treatment interval at time of onset of skin lesions	5 mg/kg (IQR 5–5.7) every 8 weeks (IQR 7–8)
Concomitant immunomodulator use at time of onset of psoriasis	N = 8 (5 azathioprine, 1 6-mercaptopurine, 2 methotrexate)

GI = gastrointestinal; IQR = interquartile range.

more recently certolizumab pegol (10–12,37,38). This paradoxical reaction is not limited to patients with IBD, but it has also been described in rheumatological conditions, including rheumatoid arthritis and seronegative spondyloarthropathies (10). The association between IBD and psoriasis is not surprising considering both conditions are associated with immune dysregulation, and TNF-α has been implicated in the pathogenesis of both CD and psoriasis (39,40). The apparent paradox lies with the development of new-onset psoriasis or worsening of existing psoriasis in the setting of TNF-α antagonist therapy because these medications are used effectively in psoriasis treatment regimens.

Reported patients with anti-TNF-α–induced psoriasis or psoriasiform eruptions are almost all adults (12). Cullen et al (14) recently presented a review of 120 cases of anti-TNF-α–induced psoriasis in patients with IBD previously reported in the literature, with the addition of a further 30 new cases. In a cohort of adalimumab-treated pediatric patients with CD, Viola et al (18) reported that 1 of 23 patients treated developed psoriasis. Hiremath et al (19) described a series of 6 pediatric patients with IBD who developed psoriasis following IFX therapy. To date there have been only a small number of published case reports and series in pediatric patients with IBD (15–17,20).

We found a prevalence of new-onset psoriasis or psoriasiform lesions of 10.5% among our IFX-treated pediatric CD population. Given the paucity of published pediatric case reports and the high prevalence in our cohort, it is likely that this adverse event is underreported in the medical literature. In a cohort of >700 IFX-treated adult patients with CD, a variety of skin eruptions, including psoriasiform lesions, occurred in 20% of patients. Almost 10% of the entire cohort, with lesions severe enough to warrant dermatology referral, was confirmed to have psoriasiform exanthemata (41). It is likely that the baseline prevalence of psoriasis among adult patients with CD without anti-TNF treatment is higher than that among children. Psoriasis prevalence rates of 10% to 11% in mainly adult patients with CD have been described (21,22); data on the prevalence of coexistent psoriasis in pediatric IBD populations are lacking. We have not formally explored the background psoriasis prevalence rate in patients not exposed to TNF-α antagonist therapy and we recognize this as a study limitation. Nonetheless, given the myriad of case reports and case series now available, this adverse event seems to be a true increase in prevalence in TNF-α–treated patients, and the Food and Drug Administration now recommends that manufacturers of TNF-α antagonist products record this on the product-prescribing information. Our experience confirms this warning to apply to children, perhaps particularly those with a positive family history of psoriasis, who in our series developed the more disturbing skin lesions.

We did not perform a skin biopsy in any of our affected patients because the clinical characteristics appeared consistent with psoriasis, and the diagnosis was confirmed in all cases by a pediatric dermatologist. Some authors have suggested that these skin eruptions are different from classic psoriasis seen in the absence of TNF-α antagonist exposure and prefer to use the term ''psoriasiform'' when describing the skin manifestations. Seneschal et al studied skin biopsy specimens from 11 patients who developed psoriasiform lesions following TNF-α antagonist therapy for various rheumatologic disorders. Although the lesions visually appeared similar to those of psoriasis, histologic features varied,

TABLE 3. IL-23 receptor polymorphism analysis

SNP (and recognized disease association)	Genotype	Infliximab-exposed patients with CD: Frequency of genotype, % Ps, n = 10	Infliximab-exposed patients with CD: Frequency of genotype, % No Ps, n = 25	OR (Ps vs no Ps) (95% CI)	Frequency of genotype, % *All patients with CD, n = 147	Frequency of genotype, % All patients with UC, n = 87	OR (CD vs UC)
rs2201841 (Ps)	GG (22)	20	12	NS	16	12	NS
rs10489628 (CD)	CC (22)	80	36	6.2 ($P = 0.03$); (1.1–36.6)	43	28	2.0 ($P = 0.017$); (1.1–3.6)
rs10789229 (nil)	AA (11)	70	24	6.3 ($P = 0.02$); (1.2–33.4)	31	37	NS
rs11209026 (Ps/CD)	GG (22)	100	100	NS	98.5	94	NS
rs1343151 (AS/CD)	GG (11)	90	44	10.2 ($P = 0.02$); (1.1–94.1)	50	43	NS

AS = ankylosing spondylitis; CI = confidence interval; CD = Crohn disease; NS = not significant; OR = odds ratio; Ps = psoriasis; UC = ulcerative colitis.
* Includes patients treated with infliximab and patients not treated with infliximab.

with spongiosus present on several specimens. Other differences included increased type 1 interferon (IFN) expression and increased expression of the chemokine receptor CXCR3 in the eruptions occurring in the setting of anti-TNF-α treatment (42).

The majority of patients reported in this case series continued IFX therapy because their skin eruptions were successfully treated with topical therapy. This is consistent with outcomes reported by Fidder et al (41), and in contrast to the findings of Rahier et al and Cullen et al (13,14), who report that up to 40% of patients with IBD developing new-onset or worsening of existing psoriasiform skin lesions discontinue anti-TNF therapy as a consequence of the adverse event.

The onset of psoriasis following TNF-α antagonists does not appear to be drug specific, and there is a risk of recurrence following instigation of an alternate anti-TNF-α agent (43). Although the majority of reported cases have been in association with IFX use, this phenomenon likely results from the earlier licensing, and hence more extensive usage, of this product. It is likely that we will see more reports of psoriasis and psoriasiform lesions with increased use of other classes of TNF-α antagonists and with the introduction of newer products.

The pathogenesis of this paradoxical process is not yet fully understood. We explored polymorphisms in the *IL-23R* gene, which is implicated in both CD and psoriasis susceptibility. IL-23 is a key proinflammatory cytokine, driving the local TH17 effector response. The binding of IL-23 to the receptor IL-23R leads to the phosphorylation of STAT3 and the subsequent expression of various IL-23–dependent genes, including IL-17A. The IL-23/TH17 axis has received considerable interest in the last few years because it is key in protective immunity against infections and pathogenic in autoimmune-type diseases such as psoriasis and CD. In such cases, tissue-derived IL-23 drives pathologic TH17 effector responses, leading to overwhelming inflammation. Genetic studies have shown that the less common A allele of the SNP rs11209026 within IL-23R confers approximately 3-fold protection against developing CD (30) and 2-fold protection against psoriasis (32). This SNP results in an arginine (R) to glutamine (Q) substitution at position 381 (R381Q) within the cytoplasmic domain of the IL-23R. Although the genetic association has been replicated numerous times, the functional consequences of carrying the protective gene variant have only recently been elucidated by Di Meglio et al. Their studies demonstrated that the R381Q protective variant negatively affects IL-23 signal transduction, reducing STAT3 phosphorylation and ultimately decreasing the amount of IL-17A produced in response to IL-23 stimulation (44); however, the frequency of this variant in the general population is low, Indeed, none of the subjects in our genetic substudy who received IFX carried this allele. Nevertheless, the findings of Di Meglio et al support the concept that IL-23 plays a major role in local tissue, rather than systemic, inflammation, and specifically that it does this by mediating the local TH17 effector response. Although R381Q is the only variant for which the precise mechanism of effect has been elucidated, multiple independent IL-23R polymorphisms have now been reported to be associated with both CD and psoriasis, suggesting a model of allelic heterogeneity where disruption of IL-23R function can occur from several distinct genetic insults. Our data were consistent with this; although the common variant for R381Q was pervasive throughout all subjects, variation within 3 of the 4 other SNPs clearly modulated a patient's risk of IFX-induced psoriasis; however, only 1 of those 3 SNPs differentiated study patients with CD from those with UC, and none of them have been previously recognized to increase the risk of psoriasis de novo. The only SNP within the study with a previously demonstrated association with psoriasis de novo had no significant association with IFX-induced psoriasis, nor did it vary between subjects with CD versus UC. The *IL-23R* is a relatively large gene. Understanding the complex, pleiotropic action of IL-23R and the specific variants that give rise to various autoimmune traits will undoubtedly increase progress in our understanding of the molecular pathophysiology underlying these chronic autoinflammatory conditions.

A Belgian group has also attempted to explore the *IL-23R* gene in patients developing anti-TNF-α–induced psoriasis/psoriasiform lesions but were unable to demonstrate an association with the *IL-23R* Arg381Gly variant (45). It is possible that the IL-23R SNPs identified in the present study represent SNPs that predispose to psoriasis (in the absence of TNF-α exposure). Evidence against this comes from Capon et al (32), who explored 2 SNPs identified in our study (rs10489628 and rs1343151) and found no difference in prevalence among patients with psoriasis and controls. The remaining SNPs identified have not been explored in psoriasis susceptibility studies to date.

Although the exact pathogenic mechanism whereby IFX induces psoriasis has yet to be elucidated, there is evidence supporting a role for increased IFN-α expression as a result of TNF-α blockade. IFN-α has been implicated in the pathogenesis of psoriasis (46). It is produced by plasmocytoid predendritic cells, which are found in increased numbers in psoriatic skin lesions. IFN-α is required for the activation of T cells in psoriatic skin lesions in an in vivo mouse model (47). TNF-α inhibits the production on INF-α by inhibiting the generation of plasmocytoid predendritic cells in vitro; it therefore seems intuitive that blocking TNF-α will lead to an increased production of INF-α (48), with the potential for psoriasis development. Our study's findings suggest that this mechanism may be further modulated in susceptible subjects via the local action of IL-23.

This case series highlights an important adverse event seen in association with IFX usage and the need for continued vigilance in all patients treated with TNF-α antagonists. We suggest early referral to a dermatologist for diagnosis and early instigation of treatment for all children with skin eruptions suggestive of psoriasis or psoriasiform eruptions while being treated with anti-TNF-α therapy. Most children respond well to topical therapy without the need to discontinue IFX therapy. We found a significant association between polymorphisms in the *IL-23R* gene and the subsequent development of psoriasis/psoriasiform lesions, and it is possible that variants in the IL-23 axis play a role in the development of this paradoxical adverse event; however, our sample size is small and therefore not adequately powered to draw any firm conclusion. In addition, DNA samples were not available on all patients described. We recognize these as study limitations. Nonetheless, we believe that our findings are hypothesis generating and warrant further exploration in large, adequately powered studies. Until further information regarding the pathogenesis of psoriasis and psoriasiform lesions in patients receiving TNF-α antagonists, it is not yet possible to identify those at highest risk and all patients should be monitored regularly for this unexpected adverse event.

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