Psoriasis and Inflammatory Bowel Disease

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Keywords

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Abstract

Background: Inflammatory bowel disease (IBD) and psoriasis (PS) are associated conditions. The reason for this association lies in the sharing of predisposition genes and common immunological mechanisms. **Summary:** This review will focus on the interplay between IBD and PS, with details on prevalence and phenotype of PS in IBD, genetics, pathogenetic pathways, and therapy. **Key Messages:** Microbiome seems relevant in both conditions: a reduction of beneficial bacteria has been observed. IBD and PS have in common some comorbidities like cardiovascular disease, similar risk of cancer and psychiatric problems. Many biological therapies such as anti-tumour necrosis factor (TNF) and anti-interleukin 23 are effective in both conditions, underlining the common immunological mechanisms. Paradoxical PS has been mainly observed after anti-TNF therapies, but preliminary reports show that it can also occur with other biologics. Genetic predisposition to this phenomenon has been reported.

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Introduction: Prevalence and Phenotype

The incidence of inflammatory bowel disease (IBD) in psoriasis (PS) is increased with a higher incidence of Crohn's disease (CD) rather than ulcerative colitis (UC). In a large prospective study of 174,476 women enrolled in the Nurses' Health Study, from 1996 to 2008, a 4.0 relative risk of CD and no increased risk of UC was observed among patients with PS [1]. As PS is more frequent than IBD (prevalence: 2 and 0.38%, respectively), there are no prospective studies that evaluated the incidence of PS in IBD. The available data deal with the prevalence of PS in IBD [2, 3]. Of course, the prevalence of PS varies in relation to the studied population: variable rates from 2 to 9% have been reported. PS have different clinical presentation: vulgaris, guttata, inversa, pustular and erythrodermic. In IBD, few studies on the clinical phenotype of PS have been carried out. Lolli et al. [4] showed, in a case-control study, that the more frequent type of PS in IBD was the PS vulgaris. Mild PS was more frequent in IBD than non-IBD (87 vs. 53%; $p < 0.0001$), whereas moderate and severe PS were more frequent in non-IBD than IBD (37 vs. 13%, $p = 0.004$; 10 vs. 0%; $p = 0.036$). Plaque-type was the most common phenotype in both IBD and non-

IBD ($p < 0.0001$ vs. others phenotypes). The frequency of plaque-type, nail PS, and psoriatic arthritis (PsA) was lower in IBD than non-IBD ($p = 0.008$; $p < 0.0001$; $p = 0.006$). Another study by Eppinga et al. [5] did not show any difference in the clinical pattern among patients with IBD and patients without IBD. The only relevant data was a more frequent use of biologics in patients with both diseases rather than those with a single disease. Among environmental factors, smoking is the most interesting one, with different association in UC, CD and PS. Indeed, smoking has been considered a risk factor for CD and a protective factor for UC [6], whereas in PS, there is a paradox: actually, in a large cohort representative of the UK general population, smoking was positively associated with PsA risk in the general population but negatively associated among patients with PS [7]. PS and IBD have common associated diseases which pinpoints the possible common pathogenetic mechanisms of the 2 conditions: arthritis is present in 30% of patients with PS and in 40% of patients with IBD [8]. Furthermore, the risk of cardiovascular disease is clearly increased in PS (hazard ratio for myocardial infarction risk in patients with PS versus general population: 1.40 [95% CI 1.09–1.80]) [9] and in IBD (hazard ratio versus controls: CD 2.89 [95% CI 1.65–5.13] and UC 2.70 [95% CI 1.69–4.35]) [10]. The risk of non-melanocytic skin tumours is increased in both the diseases, even if in IBD is correlated to the immunosuppressive treatment [11, 12]. Psychiatric involvement has also been described in both diseases, and of course this comorbidity is associated with the distorted images of bodies that both the diseases share, even if on different levels [13].

Genetics

PS and CD have a strong genetic predisposition as shown by the high concordance of the 2 diseases in twins [14–16] and by the evidence of the association with many predisposition genes [17]. It seems that for PS there is no predisposition to early disease in twins [18]. Furthermore, patients with IBD have a higher prevalence of PS in their relatives than the normal population [19]. These clinical observations have stimulated studies on the possibility of genetic sharing among the 2 diseases. Genome-wide association studies were able to identify 11 genes of predisposition common to the 2 diseases. In a large combined sample set of 6,215 CD cases, 8,644 PS cases and 20,560 healthy controls, 7 non-HLA susceptibility loci shared between CD and PS (9p24 near JAK2, 10q22 at ZMIZ1, 11q13 near PRDX5, 16p13 near SOCS1, 19p13

near FUT2, 17q21 at STAT3, 22q11 at YDJC) were identified [17]. These loci, except for SOCS1, play a role in CD aetiology, but were of unknown significance for PS. The identified shared risk loci point to very interesting functional genes that might play a role in the pathogenesis of both CD and PS. Ellinghaus et al. [20] genotyped datasets from 52,262 patients with 5 closely associated conditions (anchylosing spondylitis, CD, PS, sclerosing cholangitis and UC) and 34,213 healthy controls, being able to delineate the genetic overlap between the conditions. Their modelling supports the presence of shared pathophysiological pathways as the basis for the clinical co-occurrence, and the hypothesis that patients with concomitant syndromes are genetically distinct from patients without concomitant syndromes. Finally, Ciccacci et al. [21] found an association of TRAF3IP2 gene with cutaneous extra-intestinal manifestations in IBD.

Pathogenesis

PS has been shown to be associated with common gastrointestinal diseases (celiac disease, reflux esophagitis, irritable bowel disease) suggesting that PS is a red flag for gut inflammation in general [22, 23], even if particularly IBD and PS share the same pathogenetic mechanisms that account for the same response to drugs used in the 2 diseases. Different immunological mechanisms have been identified in both conditions [24]: (a) defective barrier and increased epithelial cell turnover with a leaky barrier function; (b) in disease lesions, proinflammatory IFN- γ -producing NK cells predominate; (c) movement of Treg cells from the circulation into the inflamed tissue contribute to the risk of the diseases; (d) Th-17 lymphocytes seem to have a central role in the pathogenesis of PS and IBD. However, unfavourable outcomes in IBD, together with the currently available anti-Th17 modalities, suggest that also the modification of the microbiome may play a relevant role [25]. Some authors [26, 27] have identified in CD a reduction of the *Faecalibacterium Prausnitzii*, a bacterium which has a beneficial role in the intestinal micro-environment. Recently, Eppinga et al. [28] identify the same reduction of concentration of *Prausnitzii* in PS, and this underlines the important role of the interaction between bacteria and immunological response. Microbiota seems to be regulated by some cytokines like interleukin-1, as reported by an interesting experimental work [29]. These observations deserve confirmation and open a wide spectrum of possible therapeutic intervention. Regarding the fact that microbiome plays a role also in PS, a

randomized placebo-controlled trial of faecal microbiota transplantation infused into the small intestine of patients suffering from active PsA who are non-responsive to methotrexate will be conducted [30]. The goal is to explore clinical aspects associated with faecal microbiota transplantation performed in patients with PsA. In this line, it is known that a Mediterranean diet may be beneficial in modifying the balance of the intestinal microflora, so it is possible to speculate that changes in the diet habits may improve the outcome of these diseases.

Therapy

Many immunosuppressive drugs have been used with success in both conditions, even if the results come from small trials or case series [31]. For example, cyclosporine has been shown to be effective in PS and in severe UC [32, 33], whereas it is not effective in CD [34]. Methotrexate has been successfully used in PsA [35] and in CD [36], but it seems poorly effective in UC [37]. The tumour necrosis factor (TNF) seems to have a relevant role in the pathogenesis of PS and IBD, as documented by controlled trials with anti-TNF in these diseases. Infliximab, adalimumab and certolizumab are able to obtain a clinical remission in both the diseases [31] (Fig. 1). Anti-Interleukin 23 has been successfully employed in the 2 different conditions. Anti-interleukin 17, which is considered useful for both conditions, at least theoretically [38], has been successful in PS [39], whereas it was not effective in CD [40] and it has also been shown to induce the paradoxical occurrence of UC [41–43]. An interesting experimental work has been conducted in mice with interleukin 35, which seems to determine remission in experimental models of colitis and PS [44]. Unfortunately, no clinical trial has been carried out with this molecule.

Paradoxical PS

In the last 10 years an increasing report of PS developing during anti-TNF treatment has been produced [45–49]. However, studies reporting psoriatic lesions induced or exacerbated by TNF- α antagonists are largely heterogeneous regarding the therapeutic agent involved, underlying disease, treatment duration, personal and family history of PS, type of cutaneous eruption, and therapeutic approaches and outcomes.

A review by Denadai et al. [45] showed that the number of cases has increased progressively from 2004 to

2011; furthermore, authors reported an experience of 222 patients with psoriatic lesions occurring during anti-TNF- α therapy. Anti-TNF- α was withdrawn in 86 patients, resulting in complete resolution of psoriatic lesions in 71 cases; anti-TNF- α was switched in 29 patients with recurrence or aggravation of psoriatic lesion in 21 cases. In 87 patients, anti-TNF- α therapy was not suspended: of these patients, 64 showed complete resolution of the lesions, 7 cases showed partially response and 2 cases did not respond. Cullen et al. [46] looked at the distribution of skin lesions among 142 patients with IBD who developed PS during treatment with an anti-TNF agent. The majority of patients had involvement in more than 1 site. Palmo-plantar areas and scalp were the most frequent sites, followed by trunk, while the facial zone was the less frequent site. The treatment of the paradoxical PS is variable according to the centre's experiences and no guidelines support the clinical decision. Following also some recently published real-life experiences on this topic [47–49], different possible approaches may be applied to handle the problem of paradoxical PS after an anti-TNF agent: (a) to stop the treatment and apply topical treatment, and successively reintroduce the same anti-TNF; (b) to use an alternative anti-TNF; (c) in the case of UC, to swap to cyclosporine; (d) to swap to ustekinumab in case of CD, or to Vedolizumab in case of UC (Fig. 2). Of course, these different approaches depend on the severity of the underlying IBD and on the response to the topical therapy or to the alternative therapies. The different outcomes indicate that a complex mechanism underlies the onset of psoriasis, rather than a simple idiosyncratic allergic reaction or sensitization to the drug. Furthermore, Vedak et al. [50] showed that there is a genetic predisposition to paradoxical PS. The mechanism of paradoxical psoriasis seems linked to the increased production of interferon, which is generally inhibited by TNF [51]. It is worthy to note here that PS has been described recently also after ustekinumab [52, 53], and after vedolizumab [50]. The pathophysiology of this paradoxical phenomenon after ustekinumab remains unknown. However, it is hypothesized that the TNF inhibitor may induce PS because of a cytokine imbalance, as interferon-alpha production by dendritic cell is normally suppressed by TNF- α 5. Similarly, ustekinumab blocks interleukin-23 activity and may decrease interleukin-23 and T helper 17 cell-induced TNF- α . In turn, interferon-alpha worsens PS by increasing promotion of T-cell activation and decreasing TNF- α 3–5 levels. As it was already described for TNF- α inhibition, paradoxical skin reactions may also occur as a consequence of a T cells misbalance induced by

Medication	Plaque psoriasis (PASI 75)*	PsA (ACR 20)†	CD (clinical remission rate)‡	UC (clinical remission rate)‡
Infliximab [◊]	FDA approved (80% week 10)	FDA approved (58% week 14)	FDA approved (49% week 6)	FDA approved (39% week 8)
Adalimumab [◊]	FDA approved (80% week 12)	FDA approved (58% week 12)	FDA approved (69% week 4)	FDA approved (17% week 8)
Golimumab	Phase III clinical trial for PsA suggests efficacy in PS (58% week 14)	FDA approved (51% week 14)	Small open-label study suggests efficacy (56% week 12)	FDA approved (46% week 6)
Certolizumab pegol	Phase II clinical trial suggests efficacy (83% week 12)	FDA approved (58% week 12)	FDA approved (48% week 26)	Small open-label study suggests limited efficacy (10% week 14)

Fig. 1. FDA-approved medication for psoriasis and/or PsA, and their evidence in CD and UC. Caution must be used when comparing PASI 75, ACR 20, and clinical remission rates among the various medications in this table, because the rates come from different studies with different trial populations and different placebo rates. Clinical remission rate may be defined differently in different studies. * PASI 75 indicates the fraction of a given population, in a given time period, that experiences a 75% or greater reduction in the PASI. † ACR 20 indicates the fraction of a given population, in a given time period, that experiences a 20% or greater improvement in swollen or tender joints in addition to >20% improvement in 3 of 5 other criteria. ‡ Clinical remission rate indicates the fraction of a given population, in a given time period, that experiences

a remission of symptoms, which is sometimes defined differently by different studies. For UC, this designation often requires a Mayo score of 2 points or lower with no individual subscore higher than 1 point. For CD, it usually requires a CDAI score lower than 150. [◊] Infliximab-dyyb (Inflectra [Pfizer, New York, NY, USA]) is a biosimilar that is FDA approved (2016) for the same indications as infliximab. [◊] Adalimumab-ano (Amjevi ta [Amgen, Thousand Oaks, CA, USA]) is a biosimilar that is FDA approved (2016) for the same indications as adalimumab. PsA, psoriatic arthritis; PS, psoriasis; CD, Crohn's disease; UC, ulcerative colitis; ACR, albumin-to-creatinine ratio; PASI, psoriasis area and severity index; CDAI, Crohn's disease activity index.

Fig. 2. Flowchart for the management of paradoxical psoriasis in IBD. If paradoxical psoriasis occurs on anti-TNF therapy, stop the treatment, apply topical treatment for psoriasis and: (a) If there is a response to topical therapy, successively reintroduce the same anti-TNF or shift to an alternative anti-TNF. (b) If there is poor response to topical therapy: (i) in case of UC, swap to Cyclosporine or Vedolizumab; (ii) in case of CD, swap to Vedolirumab or an anti-interleukin-23; (iii) in both UC and CD could shift to an al-

ternative anti-TNF. Of course, these different approaches depend on the severity of the IBD and on the response to the topical therapy or to the alternative therapies. However, the treatment of the paradoxical psoriasis is variable according to the centre's experiences and no guideline supports the clinical decision. IBD, inflammatory bowel disease; PS, psoriasis; TNF, tumour necrosis factor; UC, ulcerative colitis; CD, Crohn's disease.

$\alpha 4\beta 7$ blockade. Unlike TNF α -blockers, $\alpha 4\beta 7$ receptor blockers seem to increase the number of regulatory T cells in the skin by the increased expression of FoxP3. Furthermore, a systemic effect can be expected because it was shown that vedolizumab promotes the differentiation of Th1-cells, which in turn synthesize interleukin 10 [54].

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None.

Statement of Ethics

The authors declare that they have no ethical conflicts to disclose.

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Author Contributions

All authors contributed equally to literature search, analysis of literature, and drafting of the manuscript.

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