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Inflammatory bowel disease and psoriasis: modernizing the multidisciplinary approach

C.R.H. Hedin[1,2], E. Sonkoly[1,3], M. Eberhardson[1,4] & M. Ståhle[1,3]

From the [1]Department of Medicine, Karolinska Institutet, Solna, Stockholm; [2]Division of Gastroenterology, Medical Unit Gastroenterology, Dermatovenereology and Rheumatology; [3]Division of Dermatology, Medical Unit Gastroenterology, Dermatovenereology and Rheumatology, Karolinska University Hospital, Stockholm; and [4]Department of Gastroenterology, University Hospital in Linkoping, Linkoping, Sweden

Abstract. Hedin CRH, Sonkoly E, Eberhardson M, Ståhle M (Karolinska Institutet, Solna; Karolinska University Hospital, Stockholm; University Hospital in Linkoping, Linkoping, Sweden). Inflammatory bowel disease and psoriasis: modernizing the multidisciplinary approach (Review). *J Intern Med* 2021; https://doi.org/10.1111/joim.13282

Psoriasis and inflammatory bowel disease (IBD) are immune-mediated diseases occurring in barrier organs whose main task is to protect the organism from attack. These disorders are highly prevalent especially in northern Europe where psoriasis has a prevalence of around 3–4% and IBD around 0.3%. The prevalence of IBD in North America has been estimated at around 0.4%. The total incidence rates in northern Europe have been estimated at around 6 for Crohn's disease and 11 for ulcerative colitis per 100 000 person-years, compared with an incidence rate of around 280 per 100 000 person-years for psoriasis. Both diseases are less common in countries with a lower index of development. The rise in IBD appears to occur as populations adopt a westernized lifestyle, whereas psoriasis seems more stable and prevalence differences may derive more from variation in genetic susceptibility. The gut microbiota is clearly an important driver of IBD pathogenesis; in psoriasis, changes in gut and skin microbiota have been reported, but it is less clear whether and how these changes contribute to the pathogenesis. Large studies show that most identified genes are involved in the immune system. However, psoriasis and IBD are highly heterogeneous diseases and there is a need for more precise and deeper phenotyping to identify specific subgroups and their genetic, epigenetic and molecular signatures. Epigenetic modifications of DNA such as histone modifications, noncoding RNA effects on transcription and translation and DNA methylation are increasingly recognized as the mechanism underpinning much of the gene–environment interaction in the pathogenesis of both IBD and psoriasis. Our understanding of underlying pathogenetic mechanisms has deepened fundamentally over the past decades developing hand in hand with novel therapies targeting pathways and proinflammatory cytokines incriminated in disease. There is not only substantial overlap between psoriasis and IBD, but also there are differences with implication for therapy. In psoriasis, drugs targeting interleukin-23 and interleukin-17 have shown superior efficacy compared with anti-TNFs, whilst in IBD, drugs targeting interleukin-17 may be less beneficial. The therapeutic toolbox for psoriasis is impressive and is enlarging also for IBD. Still, there are unmet needs reflecting the heterogeneity of both diseases and there is a need for closer molecular diagnostics to allow for the development of precise therapeutics.

Keywords: psoriasis, ulcerative colitis, Crohn's disease, biologic drugs.

Introduction

Inflammatory bowel disease (IBD) and psoriasis are chronic inflammatory conditions with a lifelong relapsing–remitting course. The prevalence of psoriasis amongst patients with IBD is increased compared with the background population, and similarly, patients with psoriasis have increased risk of developing IBD, with particular association between psoriatic arthritis (PsA) and IBD [1]. Both IBD and psoriasis require treatment, often with immunosuppressant drugs with substantial overlap in the effective drugs between the two conditions. The development of potent-targeted therapies is changing the outlook for chronic inflammatory diseases such as IBD and psoriasis. Moreover, the increasing array of available drug treatments has brought about a scenario where physicians can select treatments specifically optimized for the patient. In this situation, the presence of multifocal

inflammation can be critical in determining the optimal treatment. However, the situation is not as simple as selecting a drug shown to be effective for all the inflammatory conditions in a given patient: paradoxical inflammation at a site distant from the initial inflammatory condition may be induced by biologic therapies. Furthermore, research into the molecular drivers of chronic inflammation, many of which are common to different conditions, opens up the possibility that traditional organ-based classifications may give way to a molecular taxonomy of chronic inflammatory disease. Such molecular characterization may in the future underpin therapeutic decisions. In this clinical era, the partnership between different organ-based specialists becomes more important and collaborative therapeutic decision-making has become more common. Because of this clinical need, many centres have instigated cross-speciality conferences as a cooperative forum. This article sought to bring together the knowledge in the pathogenesis and treatment of psoriasis and IBD to enable effective collaboration between physicians from different specialities.

Clinical presentation

Psoriasis is characterized by inflammatory hyperproliferation of keratinocytes, impaired barrier function of the skin and infiltration of activated immune cells. IBD is also characterized by impaired barrier function of the gut and infiltration of both innate and adaptive immune cells leading to inflammation of the gut mucosa with ulceration and fibrosis. In both psoriasis and IBD, inflammatory symptoms may fluctuate substantially during life with many patients experiencing periods of near or complete remission between disease flares. The disease spectrum is wide with great variation between affected individuals with very mild to severe and incapacitating disease. The onset of both psoriasis and IBD is typically at a young age with peak onset around 15–30 years, but either can start at any age. Both IBD and psoriasis tend to be more aggressive in those with paediatric onset. In psoriasis, the predominant phenotypes are as follows: plaque psoriasis (75–80%) with red, scaly and sharply demarcated skin lesions developing in typical locations such as scalp and extensor surfaces (Fig. 1); and guttate psoriasis (15–18%) with sudden onset of widespread smaller, scaly lesions typically following a throat infection. Rare and severe phenotypes are erythrodermic and pustular psoriasis. The basis for phenotypic variation is not clear but likely reflects variation in underlying genetics [2]. The phenotype of IBD is traditionally divided into ulcerative colitis (UC), which causes mucosal colonic inflammation continuously and proximally from the anus, and Crohn's disease (CD), which causes inflammation discontinuously and affecting any part of the gastrointestinal tract. Moreover, CD may be associated with stricturing or penetrating behaviour with the formation of abdominal and perianal fistulae and abscesses. There is increasing evidence including both genetic [3] and microbiological methods that the traditional division between CD and UC may not reflect the true underlying pathogenesis and the different phenotypes likely overlap on a spectrum of disease.

Associated inflammatory conditions

Psoriasis and IBD are both associated with a range of other inflammatory comorbidities (a clinical phenotype that may be termed multifocal inflammation) but with different profiles. Arthropathy occurs in both conditions, and PsA develops in 30% of patients with psoriasis [4]. In contrast to IBD, psoriasis is also highly associated with vascular inflammation and lipometabolic disease such as obesity, hypertension, diabetes and cardiovascular disease [5]. These are comorbidities that parallel disease severity whilst also driving the inflammation. Overall psoriasis is today considered a systemic inflammatory disease with comorbidities affecting many organ systems. The prevalence of psoriasis in patients with IBD was 1.2% in a recent meta-analysis [1].

Up to 50% of patients with IBD develop extraintestinal inflammation [6], with the most common being spondyloarthopathies, primary sclerosing cholangitis, ocular inflammation such as anterior uveitis, and skin inflammation including erythema nodosum, pyoderma gangrenosum and psoriasis [7]. The prevalence of arthritis in patients with IBD is somewhat lower than in patients with psoriasis: radiological evidence of sacroiliitis occurs in 20–50% of patients with UC and CD, but progressive ankylosing spondylitis occurs in only 1–10% of patients [7]. The prevalence of psoriasis in patients with IBD is between 3 and 4%, with the prevalence slightly higher in patients with CD [1]. Interestingly, CD itself can affect the skin both adjacent to the gut (perianal disease) and, more rarely, in areas remote from the gut. The immunological mechanisms that might underlie multifocal inflammation fall into two broad categories: multifocal inflammation may arise from an extension of antigen-specific immune responses from the one site to another; and

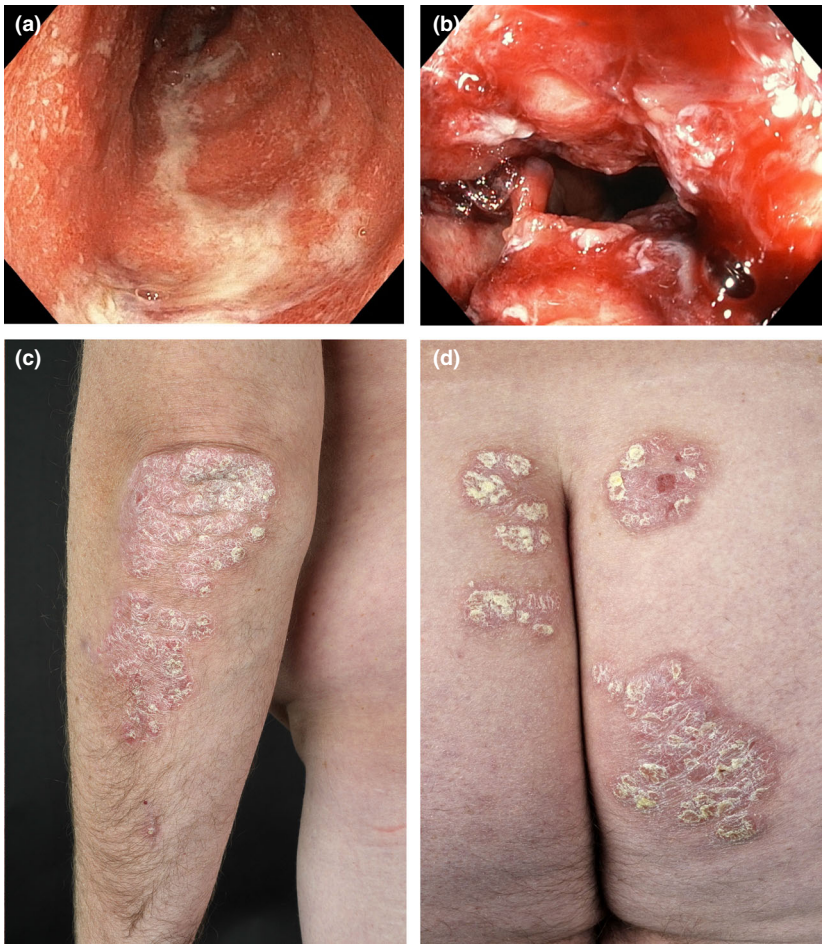

Fig. 1 *Clinical presentation of IBD and psoriasis: (a) Endoscopic picture of ulcerative colitis showing continuous inflammation, marked erythema, lack of vascular pattern, erosions and longitudinal ulceration. (b) Endoscopic picture of an inflamed colonic stricture in a patient with Crohn's disease showing luminal narrowing, deep ulcerations and spontaneous bleeding. (c and d) Classic plaque psoriasis lesions in a middle-aged man showing sharply demarcated scaly red lesions on extensor surfaces. All images reproduced with patients' permission.*

alternatively, inflammation at separate sites may be independent inflammatory events initiated or perpetuated by shared genetic or environmental risk factors in the host [8]. These mechanisms are not mutually exclusive and may contribute to varying degrees in different clinical phenotypes. However, analysis of shared genetic risk loci across a variety of clinical phenotypes has implied that multifocal inflammation may be genetically distinct unifocal or single-organ inflammation [9].

Pathogenesis

The current paradigm of the pathogenesis of IBD describes an aberrant immune response against the commensal gut microbiota in a genetically susceptible host after (often as yet unidentified) environmental triggers. Similarly, in psoriasis genetic predisposition combined with environmental factors leads to an abnormal immune activation in the skin. In recent decades, knowledge about the pathogenesis of both diseases has rapidly increased as a result of a fruitful dialog between basic immunological research and clinical experience with targeted therapies.

Epidemiology

Psoriasis appears to affect men and women broadly equally [2]. Similarly, the overall incidence of IBD is

comparable between the sexes although the relative frequency of diagnosis of CD and UC may vary according to sex at different ages [10]. This is in contrast to many other autoimmune diseases that show a female preponderance [11]. For both IBD and psoriasis, there is geographic variation with higher disease incidence in Europe and North America and lower incidence rates in Asia and the Middle East [12, 13]. For IBD, the increase in incidence appears to occur in conjunction with industrialization – that is, those countries with later industrialization have experienced increased incidence more recently [14]. In comparison, there is little evidence that psoriasis is increasing in association with adoption of a westernized lifestyle despite the influence of risk factors such as obesity and smoking. However, such data should be interpreted with caution; particularly as for psoriasis, the true prevalence is difficult to estimate as many individuals have mild disease and may be under the radar for the healthcare system.

Migration studies indicate that first-generation immigrants retain the risk for IBD associated with their country of origin, whereas second-generation immigrants take on the incidence as seen in their country of birth [15, 16]. Moreover, a north–south gradient has been demonstrated within countries for IBD [17, 18] and to a lesser extent for psoriasis [19]. The explanation for these observations is not clear but implicates environmental factors such as climate, diet (particularly vitamin D), economic or other influences.

Genetics

Despite the evidence of the role of environmental factors, it is clear that genotype underpins the risk for IBD and psoriasis. Psoriasis concordance in monozygotic twins (33–50%) is greater than in dizygotic twins (10–17%) [20-22], with similar observations for IBD (monozygotic concordance: 30% for CD and 14% for UC; dizygotic concordance: 2% for CD and 6% for UC) [23]. One of the greatest risk factors for developing IBD is having a first-degree relative with IBD [24, 25], with the risk of developing IBD in siblings of patients with CD around 5% [26]. Similarly, the lifetime risk of psoriasis increases with the number of affected relatives, being 25 % with one affected sibling or parent and up to 50% with 2 affected close relatives [27]. Both IBD and psoriasis are more common in people of European ancestry [28, 29]. Specific ethnic groups have a markedly increased risk for IBD, for example Ashkenazi compared with Sephardic or Oriental Jews [30]. Equivalent groups with particularly increased risk of psoriasis have not been described; on the other hand, there are specific ethnic groups with particularly low prevalence of psoriasis such as the Inuit population of Greenland [31].

More recently, GWAS with large patient cohorts has led to the identification of new psoriasis susceptibility genes with functions including antigen presentation, specific cytokines and their cytokine receptors, downstream inflammatory signalling pathways and epithelial functions [32-34]. Similarly, GWAS have uncovered many novel IBD pathways including innate immunity, T-cell activation and differentiation, T- and B-cell regulation, epithelial barrier function and repair, and NF-κB and IL-23 pathways [35, 36]. Several genetic susceptibility regions are shared between psoriasis and IBD [37, 38], including 1p31.1 harbouring the *IL-23R* where the common locus involves a shared protective polymorphism, but with different risk variants. In a large cohort of patients, 11 susceptibility loci common to IBD and psoriasis were identified: seven outside the human leucocyte antigen region and four previously established psoriasis and CD risk loci [39]. These overlapping loci include *ZMIZ1,* which encodes for the protein zinc finger MIZ type 1 that regulates the activity of several transcription factors including Smad3/4 and p53, and TGF-β/SMAD signalling, and is induced by retinoic acid. Suppressor of cytokine signalling 1 (*SOCS1*) was also a shared locus for CD and psoriasis: this gene encodes a protein that is a member of the STAT-induced STAT inhibitor family. Cytokines such as IL-2, IL-3, erythropoietin and interferon-gamma can induce expression of SOCS1, which in turn may then negatively regulate other cytokines.

A large cohort of >86 000 individuals was achieved by collaboration between 5 different consortia and used high-density genotype data to identify independent multidisease signals [9]. Analysis of the genetic relationships between diseases implicated the presence of shared pathophysiological pathways as the basis for the co-occurrence of distinct clinical inflammatory phenotypes (multifocal inflammation). Moreover, these data supported the hypothesis that patients with multifocal inflammation are genetically distinct from patients with unifocal or single-organ inflammation. Of note, this study also linked identified genes to

potential drug discovery motivating the exploration of novel drugs such as CCR2 antagonists (MLN-1202) and CCR5 antagonists (INCB9471 and AMD-070) as potential new treatments of inflammatory diseases including CD, UC and psoriasis.

Epigenetics

Despite the numerous disease-associated variants identified in chronic inflammatory diseases such as IBD and psoriasis, they cumulatively explain only a small proportion (<28%) of the heritability [9, 40]. Many of the polymorphisms associated with IBD and psoriasis are located in noncoding regions of the genome, and these, along with DNA methylation and histone modification, may in part account for the missing heritability [41]. Epigenetic mechanisms alter gene expression without changing the underlying DNA sequence; some examples include DNA methylation, histone modifications and non-coding RNA-mediated gene regulation. Crucially, these epigenetic factors represent a substrate for the interaction between genetic and environmental risk factors. In one study, 92 of the known IBD risk loci were associated with regulatory elements [42], and this in turn implicates the genes that these regulatory elements control. DNA methylation is extensively altered in psoriatic skin [43], and of note, changes in DNA methylation have been observed even in the uninvolved skin of patients with psoriasis [44]. In addition, the majority of the non-protein-coding genome is transcribed and gives rise to noncoding RNAs, which regulate the expression of other genes. Noncoding RNAs, in particular, miRNAs, have been implicated in the pathogenesis of psoriasis, and modulation of their expression represents a potential novel therapeutic strategy [40, 45]. The extent to which epigenetic links may underlie the clinical relationship between IBD and psoriasis and potentially provide insights into future treatments is as yet not fully explored.

Environment

Several environmental factors that are important for the onset of IBD have been identified including birth order [46], smoking [47], breastfeeding [48] and antibiotic exposure in childhood or in utero [49, 50]. Notably, many of the risk factors identified from epidemiological studies could have their impact through effects on the acquisition/ development of gut microbiota. Indeed, alterations in the gut microbiota in healthy children related to exposure to these environmental factors have been demonstrated [51]. For psoriasis, the relative contribution of the environment is less, and the relevant factors are less well delineated. Stress, infections and some drugs have long been known as triggers of psoriasis, whilst obesity and smoking increase the risk of developing psoriasis, but little is known about the mechanisms through which these factors act [2, 52].

Microbiota

The central role of the intestinal microbiota in the pathogenesis of IBD is clear. Diversion of the faecal stream results in resolution of gut inflammation [53], many animal models of IBD are dependent on the presence of the gut microbiota [54, 55]. A gut–skin–joint axis has been proposed to explain the relationship between changes in the gut microbiota, increased intestinal permeability and altered immune homeostasis that may contribute to skin and joint inflammation; however, more evidence is needed to confirm and explore these associations [56]. For the identification of specific microbial species, the research field suffers from differing study designs and varying microbiological methods. Nevertheless, overall lack of diversity appears to be a feature of an unhealthy gut microbiota [57]. Some generalizable results in IBD have been described: butyrate producers such as *Faecalibacterium* prausnitzii and Roseburia spp and other short-chain fatty acids are reduced, whereas mucin degraders such as adherent-invasive *Escherichia coli* and *Ruminococcus gnavus* are increased in patients with IBD [58, 59]. In contrast, *Akkermansia muciniphila*, a mucin degrader, has been shown to be decreased in IBD [60]. The role of microbiota is less clear in psoriasis. The abundance of *A. muciniphila* has been demonstrated to be reduced in patients with psoriasis [61], and a study in IBD and psoriasis found reductions in *F. prausnitzii* in both conditions but not in hidradenitis suppurativa [62]. However, in a recent study psoriasis patients' gut microbiota was characterized by large increases in *Akkermansia*, *Faecalibacterium* and *Ruminococcus* and a decrease in *Bacteroides* compared with healthy controls [63], a pattern that contrasts with that described in IBD. The composition of the skin microbiota is changed in psoriasis as compared to healthy skin; however, it is as yet unclear whether these changes are of pathogenic significance or just a consequence of chronic skin inflammation [64]. However, in one study the presence of *Corynebacterium* spp was negatively associated with co-expressed genes involved in interferon signalling, suggesting a

potentially protective role [65]. This last observation raises the possibility of pathogenically relevant cutaneous microbial changes in psoriasis.

Diet

Diet is a key modulator of the gut microbiota. This observation coupled with patients' desire to manage disease through diet has prompted a variety of studies of dietary management of IBD and the role of diet in IBD pathogenesis. For example, adherence to a traditional Mediterranean diet (including legumes, fruit, vegetables, nuts, fermented dairy products) has been associated with a lower risk of developing CD [66]. In terms of disease management, IBD patients with strictures are advised to follow a diet lower in fibre, and in paediatric IBD, there is good evidence for the effect of exclusive enteral nutrition (EEN) in treating acute disease flare [67]. EEN is a difficult diet to follow as it comprises only nutritional drinks, so alternatives such as the Crohn's Disease Exclusion Diet, which also includes some regular foodstuffs, have been tested with some success [68]. Several nutrients such as omega-3 fatty acids [69], red/processed meat [70] and fructo-oligosaccharides have been identified to have a role in gut inflammation in preclinical studies but have not translated into demonstrable benefit in clinical trials [71]. Otherwise, there is not yet adequate evidence to recommend a specific diet for the management of IBD apart from the general advice to eat a varied diet, high in fresh, plant-based ingredients with an avoidance of highly processed food. The impact of diet on psoriasis is controversial. A systematic review from the National Psoriasis Foundation [72] based on 55 studies concluded that dietary weight reduction with a hypocaloric diet in overweight and obese patients is strongly recommended; however, similar to the situation in IBD for most studies the level of evidence is too low to support specific dietary recommendations. Interestingly, there is an association between psoriasis and coeliac disease [73], and in patients positive for anti-gliadin and with high transglutaminase titres, improvement in skin lesions may occur with gluten-free diet [74].

Smoking

Smoking has been linked to a number of immune-mediated/inflammatory diseases, including psoriasis and CD. Smoking is associated with an increased risk of developing psoriasis and is also associated with more severe psoriasis and poorer response to treatment; [75, 76] however, mechanisms are not defined. Interestingly, smoking is also positively associated with PsA; however, amongst patients with psoriasis, smoking decreases the risk for development of PsA, referred to as the 'smoking paradox' [75]. There is also a paradoxical association between smoking and IBD with smoking positively associated with CD [77] but negatively associated with UC [78]. Smoking is also associated with lack of response to anti-TNF in patients with CD [79]. Smoking is also associated with increased risk for some of the known comorbidities of psoriasis, primarily cardiovascular disease. Moreover, smoking appears to enhance the risk for inflammatory skin disease and joint disease in patients with IBD; [80] therefore, smoking cessation programmes are a key feature for the management of psoriasis, PsA and CD.

Key cytokines

Many genetic risk loci linked to autoimmune diseases code for cytokines and their receptors such as interferon-γ, IL-10, IL-22, IL-23 and the IL-23 receptor. The identification of disease-associated cytokines has provided a basis for the development of antibody-based biologic drugs [81-83]. However, demonstration of the role of specific molecules in pathogenesis does not always translate into therapeutic efficacy. TNF-α is a cytokine with broad proinflammatory effects and is a central target for inhibition in multiple immune-mediated diseases such as IBD, psoriasis, PsA and spondyloarthritis. In contrast, inhibition of other cytokines with broad proinflammatory effects such as IL-1β and IL-6 (canakinumab and tocilizumab) is not efficacious in healing intestinal or skin inflammation. IFN-α is involved in the initiation phase of psoriasis; however, its inhibition has not shown efficacy most likely because the role of this cytokine is limited in established disease [84]. IL-23 is produced by dendritic cells and promotes Th17/Th22 cell proliferation and activation, which in turn produce IL-17 and IL-22; this is a central pathway in the pathogenesis of psoriasis, as evidenced by the efficacy of biologic treatments targeting this pathway in UC, CD and psoriasis (Fig. 2). In contrast, inhibition of IFN-γ, the main cytokine produced by Th1 cells, showed only moderate effects in psoriasis, despite the strong IFN-γ signature in psoriasis skin lesions [85, 86]. IL-17A, the signature cytokine of Th17 cells, is highly expressed both in psoriasis and in IBD. However, inhibition of IL-17A or its receptor showed clearly different effects in psoriasis and IBD – whilst anti-

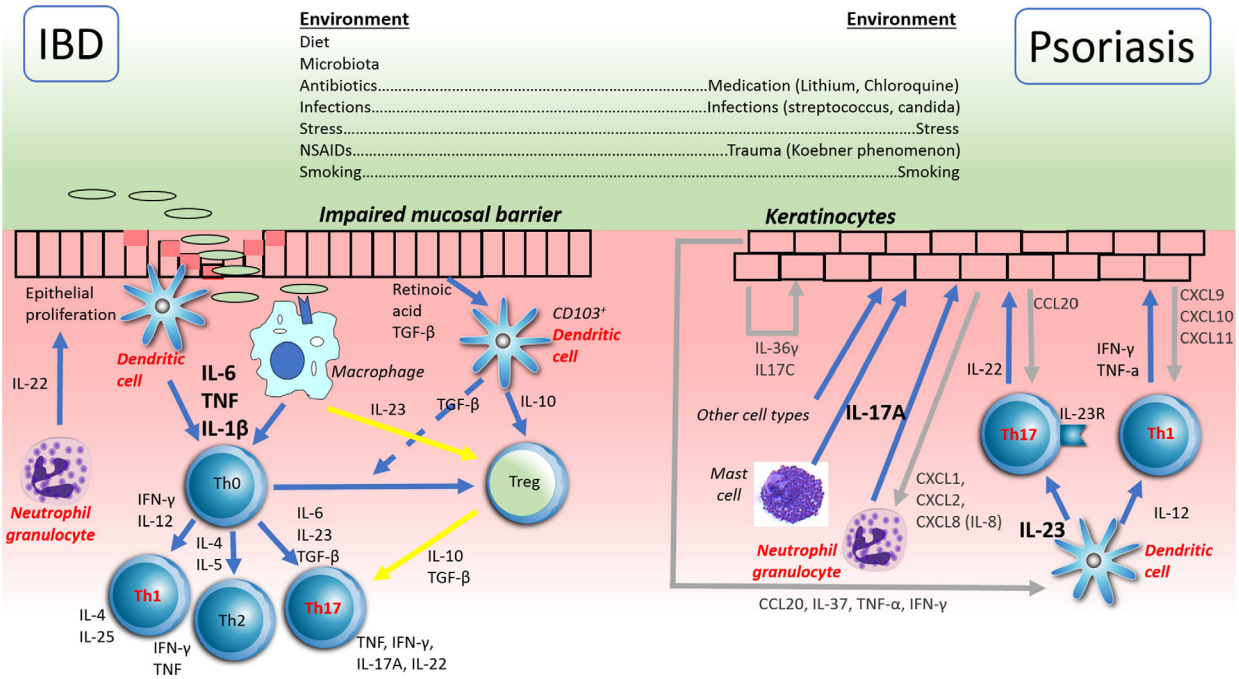

Fig. 2 *IBD and psoriasis share immunological 'triggers'. Common inflammatory cells are marked in red. In the immunopathogenesis of psoriasis, chronic inflammation is maintained by disturbed interaction between infiltrating immune cells and the epithelial cells of the skin, keratinocytes. A central driver of inflammation in psoriasis is the IL-23/Th17/IL-17 axis, as also evidenced by the high efficacy of biologic treatments specifically targeting this axis. In the immunopathogenesis of inflammatory bowel disease, microbiota crossing the intestinal barrier is probably a primary driver for the continuous T-cell response mediated by different antigen-presenting cells in the gut.*

IL-17A/IL-17RA is efficacious in psoriasis and PsA, clinical trials with IL-17A/RA inhibition in CD showed no benefit and in some cases even led to exacerbation of the disease [87]. The most likely explanation is that Th-17 has an important physiological function in the gut, seeming to promote barrier integrity and immunological balance, by IL-22 production and enhancing antimicrobial peptide secretion and tight junction expression [88, 89].

Further, many anti-inflammatory cytokines are fundamental for immunological homeostasis and healing. In the intestine, IL-10 and TGF-β from T-regulatory cells and IL-22 produced by Th17 cells and innate lymphoid cells (ILC) are important in promoting mucosal restitution. IL-10 receptor mutations cause infant-onset severe CD that may require haematopoietic stem cell transplantation. However, modifying the IL-10 or TGF-β pathways in clinical trials has not proven efficacious in IBD. IL-22, similar to IL-17, seems to have divergent roles in gut and skin. This cytokine is important for gut homeostasis and epithelial regeneration, whilst in psoriasis, elevated IL-22 is pathogenetic, inducing the characteristic epidermis thickening.

Common mechanisms

As discussed above, there are several proposed common mechanisms in the pathogenesis of IBD and psoriasis. Lifestyle factors such as obesity and smoking are important in both diseases. Genetic overlap in the pathogenesis of IBD and psoriasis has been identified as described above, and this genetic link is evidenced by the higher rate of psoriasis in relatives of patients with IBD and vice versa [90]. However, the extent to which epigenetic links may underlie the clinical relationship between IBD and psoriasis is not yet fully elucidated. Gut microbial antigens are clearly critical in the pathogenesis of IBD as discussed above, patients with psoriatic arthritis have also been shown to have decreased faecal microbial diversity [91], and levels of faecal Saccharomyces cerevisiae have been shown to be decreased in psoriasis patients compared with

healthy controls [92]. However, focussing on the existence of common microbial antigens between IBD and psoriasis probably belies a much more complex role for the microbiota in the regulation and conditioning of immune responses both within and outside of the gut.

In contrast, although the rise in IBD incidence appears to follow the adoption of a westernized lifestyle, this appears not to be as important in the pathogenesis of psoriasis. Moreover, evidence to support the pathogenic role of a range of specific dietary factors is accumulating in IBD as described above, whereas the literature in psoriasis implicates the caloric content of the diet and obesity. This may reflect a difference in the importance of diet in pathogenesis between the two diseases, although it may also reflect the fact that diet is often a focus for patients with gastrointestinal symptoms, prompting more research in this area.

Both in psoriasis and in IBD, a combination of genetic/epigenetic and environmental factors leads to immune activation in the affected tissue. In both conditions, TNF-a and IL-23 seem to have an important role in promoting inflammation, whilst the roles for other inflammatory mediators such as IL-17 and IL-22 differ in psoriasis and IBD, which is also reflected in response to targeted treatments.

Clinical management

Treatments

IBD

Conventional IBD Treatment. Currently, IBD cannot be cured, but many patients with IBD can be brought into prolonged remission with long-term medication. Glucocorticosteroids are a mainstay for flaring IBD and can be administered locally, orally and/or intravenously. Therapeutic effects are mediated through glucocorticoid receptors, which bind to glucocorticoid-responsive gene elements, inducing anti-inflammatory proteins and inhibiting proinflammatory cytokines such as IL-1, IL-2, IFN-γ and TNF-α and downregulating NF-κB [93-96]. The second pillar of acute IBD therapy is 5-aminosalicylate (5-ASA) drugs, which can be used locally and/or orally in high doses for induction of remission and lower doses for maintenance. Aminosalicylates reduce mucosal IL-1β, IL-2 and IFN-γ, prostaglandins, leukotrienes and NF-κB. Besides modulating the RelA/p65 phosphorylation, 5-ASA probably also activate the PPAR-γ receptor, thereby inhibiting the expression of IL-1β and TNF-α. PPAR-γ also impedes proliferation of intestinal immune cells through apoptosis [97, 98].

Antimetabolites. Thiopurines (azathioprine and 6-mercaptopurine) interfere with cell replication via their metabolite 6-thioguanine, which replaces guanine in replicating DNA [99, 100]. Further downstream, the metabolite 6-thioguanine-triphosphate (6-TGTP) also promotes apoptosis of T cells by blocking Racl signalling induced by CD28 stimulation, which may explain the delayed onset of clinical response (up to 3 months) associated with thiopurine treatment [101]. Another cancer drug, methotrexate, inhibits folic acid metabolism, leading to decreased conversion of homocysteine to methionine and suppression of lymphoproliferation [102]. Studies have also identified decreased synthesis of purine sand cytosolic accumulation of adenosine, which results in decreased levels of TNF-α and membrane IL-2 receptors on T cells [103]. The use of antimetabolites is limited to maintenance treatment due to the delayed therapeutic effect.

Monoclonal antibodies. Monoclonal antibodies have revolutionized the treatment of systemic inflammation and are used to suppress acute inflammation and maintenance therapy. Anti-TNF-α antibodies (infliximab, adalimumab, golimumab) were the first to show convincing clinical efficacy in IBD, targeting soluble TNF-α (sTNF) and its transmembrane precursor (tmTNF) [104] (Fig. 3). Besides neutralizing TNF-α, the aggregation of anti-tmTNF-bound antibodies on immune cells results in antibody-dependent cell-mediated cytotoxicity (ADCC) and complement cascade activation leading to T-cell death. Second generation of antibodies in IBD targets α4β7 integrin expressed by gut-homing B and T cells [105]. The α4β7 integrin mediates extravasation through its endothelial ligand MAdCAM-1 and mediates migration to the inflammatory site. Vedolizumab specifically targets the α4β7 heterodimer, thereby upholding gut specificity [105]. Ustekinumab, a monoclonal antibody against the p40 subunit common to both the IL-12 and IL-23 cytokines, is an established therapy for psoriasis and PsA by blocking these cytokines that promote Th1 and Th17 responses. This antibody has also proven efficacious for both CD and UC [106].

JAK inhibitors. The intracellular tyrosine kinases, Janus kinase (JAK)1, JAK2 and JAK3, and tyrosine

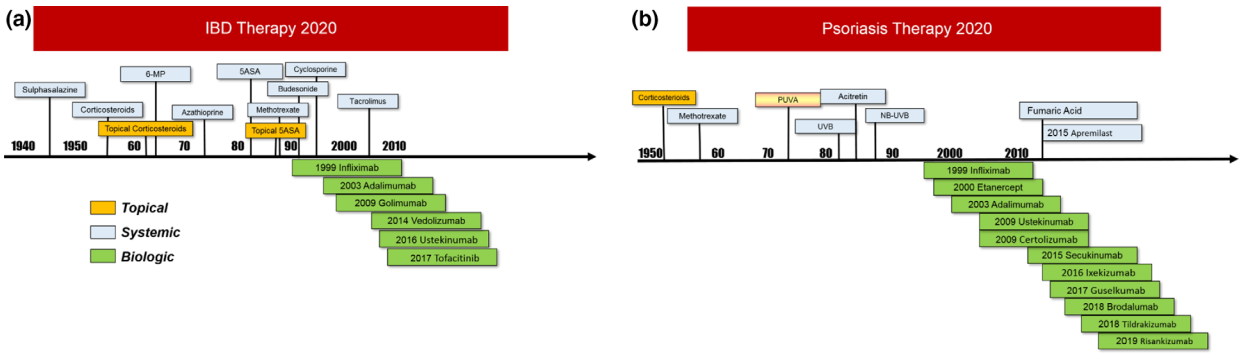

Fig. 3 *(a) Timeline of the approximate date of introduction of drugs for use in IBD. (b) Timeline of the approximate date of introduction of drugs for use in psoriasis.*

kinase 2 (TYK2), regulate a broad range of different cellular functions such as activation, proliferation, differentiation and migration. JAK pathways are important in activating and maintaining inflammation through lymphocytes and production of antibodies. Tofacitinib is an orally administered small molecule that inhibits various JAKs, targeting both the innate and adaptive immune system, and has efficacy in PsA and UC. However, tofacitinib has not shown significant efficacy in the CD trials [107].

Psoriasis

Psoriasis is highly heterogeneous, with the majority of patients exhibiting mild disease. For these, topical agents remain the mainstay of treatment, including topical corticosteroids and vitamin D analogues often in combination with natural sunlight or ultraviolet (UV) therapy. For the 20- 30 % of individuals with more severe psoriasis, therapeutic options have changed and improved radically over the past decades (Fig. 3).

Traditional systemics. Methotrexate has been used for treatment of psoriasis and PsA for decades and is still widely used. For patients with moderate disease activity, it may be sufficient to control symptoms. Potential hazards include liver and bone marrow toxicity, and medication requires close monitoring. The vitamin A analogue, acitretin, was introduced in the 70s. Its role is diminished in favour of newer, less teratogenic drugs, but it may be indicated in, for example, pustular psoriasis. Ciclosporin is highly effective and is currently used mostly as rescue over the short term since long-term use is associated with nephrotoxicity.

Biologics. The introduction of monoclonal antibodies targeting cytokines with a central role in psoriasis pathogenesis has completely changed the outlook for patients. Starting with drugs blocking TNF-α and subsequently moving on to more specific targets such as IL-17 and IL-23 has provided a versatile toolbox for dermatologists, and the majority of patients with extensive skin disease now achieve almost complete relief of symptoms, albeit not cure (Fig. 4). For these targets, several antibody options are available, as well as drugs targeting their receptors. The main obstacles today are rare phenotypes such as pustular psoriasis and multifocal disease such as concomitant arthritis or IBD where therapies may not work equally well in both conditions. Also, treatment is generally standardized and not individualized since biomarkers are lacking and clinical trials focus on patients with common plaque psoriasis. Overall, biologics appear to be relatively safe and are closely supervised with data from long-term registries monitoring potential toxicity and adverse effects. Cost is a big problem preventing access, but the introduction of biosimilars is helpful.

The drug pipeline psoriasis is ongoing, and biologics are not the end of the road. Small molecules targeting intracellular pathways such as JAK-STAT are promising, and such drugs may also form the basis for much needed new topical therapies [108].

Practice similarities

Despite the impressive progress in our understanding and treatment of immune-mediated inflammatory diseases, substantial challenges remain. In this respect, we see not only many similarities but also differences between IBD and psoriasis.

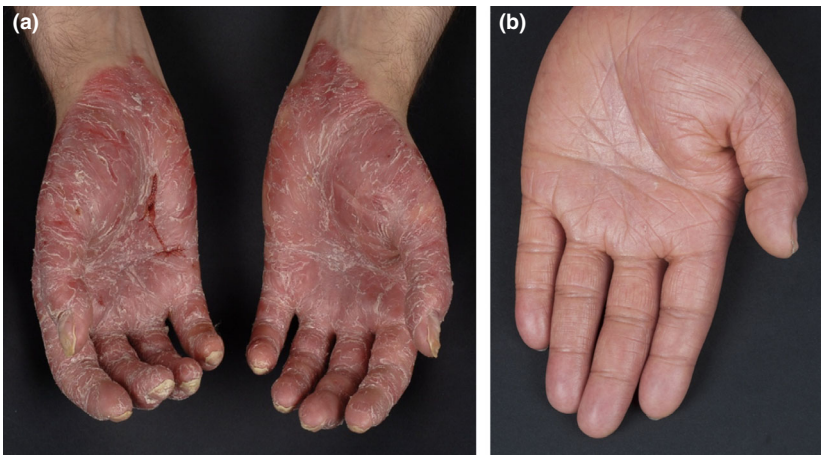

Fig. 4 *Palmar psoriasis before (a) and after (b) 3-month treatment with anti-TNF biologic therapy.*

Prognostic indicators

Clinical phenotyping and diagnosis rely predominantly on parameters that are obvious to the eye but lack deep molecular and genetic fingerprinting. Conversely, molecular studies have revealed subgroups of patients who had not previously been appreciated [109]. In the IBD and psoriasis, current clinical phenotypes harbour a collection of biologic variations with differences in severity, prognosis and therapeutic response. However, robust diagnostic biomarkers are still lacking; this is an area that merits further research and where we can expect real progress.

An important aspect of management in both IBD and psoriasis is early identification of patients who will go on to have an aggressive disease course, offering the potential for early and targeted interventions. This may both prevent suffering and organ damage and protect patients from unnecessary exposure to drug side effects. Since the first recognition of IBD as a clinical entity, phenotypic features associated with poor prognosis have been identified [110]. However, there are limitations to the accuracy of phenotype-based disease course prediction, and therefore, prognostic biomarkers associated are being actively sought.

Biomarkers

Identification of clinical and molecular biomarkers requires structured medical surveillance and analysis of genetic, epigenetic and clinical data in stratified patient populations. So far, there are very limited data, but current technological explosion in analysing big data offers new potential. Here, the role of the clinician in careful phenotyping emerges as critical to facilitate relevant stratification of patient populations. In IBD, frequently relapsing disease has been predicted using $CD8^+$ T-cell gene expression profiling [111, 112]. This profile corresponds to 'T-cell exhaustion' whereby T cells lose their capacity to respond to antigen over time. Prognostic value has also been found for faecal markers such as calprotectin and lactoferrin [113, 114], and serological markers targeting autoantigens (such as perinuclear antineutrophil cytoplasmic antibodies) or microbial antigens (such as anti-Saccharomyces cerevisiae antibodies) [115-117]. Tissue-based markers have also had some success; for example, the gene expression signature from ileal biopsies in children has been associated with risk for fistulizing disease in CD [118]. In chronic disease with heterogeneous natural history, the use of biomarkers to stratify patients will be a key feature of personalized treatment.

Top-down versus step-up strategies

In both psoriasis and IBD, the traditional treatment paradigm has been a stepwise procedure starting with the least potent therapies, which are also usually the safest and stepping up the therapeutic ladder to more potent therapies with associated increased risks (the 'step-up' approach). Early initiation of aggressive therapy in selected patients has been advocated – the 'top-down' approach – with the aim of suppressing the initial

inflammation and preventing chronicity [81, 119, 120]. Implementation of this strategy faces significant hurdles such as early diagnosis and reliable prognostic markers. However, it has been speculated that early intensive treatment could alter the disease course ('disease modification') and ongoing studies may prove – or disprove – this hypothesis [81]. The post hoc analysis of clinical trials in IBD has provided evidence to support this hypothesis; for example, in CD higher rates of remission were seen in patients starting adalimumab within 2 years of diagnosis compared with those starting adalimumab > 5 years after diagnosis [121], and lower risk for intestinal strictures was demonstrated in CD patients with early introduction of immunomodulators or biologics [122]. However, although the benefit of top-down strategy in IBD was demonstrated as early as 2008 [120], it has not yet gained traction in most clinical settings, largely due to economic limitations and lack of clinically available prognostic biomarkers.

Secondary loss of response

Secondary loss of response to biologic drugs occurs when a patient with initial good response to a drug subsequently develops symptoms attributable to the initial inflammatory diagnosis whilst still on the drug. This occurs in 13-20% of patients with IBD per year [123, 124] and can be caused by subtherapeutic drug levels secondary to the development of anti-drug antibodies (ADA) [125]. The immunogenicity of nonhumanized infliximab may be higher than that of other biologics [126, 127], so in order to prevent ADAs, many patients treated with infliximab also receive concomitant thiopurines, which appear to inhibit the formation of ADA and result in higher concentrations of the biologic drug [128-130]. However, combination therapy entails enhanced infectious and neoplastic risk. In clinical practice, patients with IBD who experience disease relapse on biologic drugs are often tested for evidence of ADA with subsequent optimization of the biologic dose or addition of an immunomodulator in the hopes of recapturing response. For patients who ultimately do not regain response to their first drug, these manoeuvres may entail delay before switching to an effective therapy. However, this strategy is pursued in most IBD centres primarily because of the limited range of alternative drugs, which drives a desire to 'get the most' out of each drug before switching. In psoriasis, the majority of patients can achieve clear or almost clear skin after 12–16 weeks on a biologic; however, loss of response over time is relatively common and may necessitate switching to another biologics. The mechanisms behind secondary failure in psoriasis are not fully understood, and there are no predictive biomarkers. The strategy for dealing with secondary loss of response in psoriasis differs from IBD with less focus on optimization of the current drug and more ready switching to an alternative. Previously, when psoriasis treatment was more reliant on infliximab, then ADA testing and drug optimization were the more common practice. However, the greater availability of alternatives results in less delay before disease control is regained. Although in IBD the therapeutic arsenal is increasing, for a long time, there was no alternative to anti-TNF and the traditions of clinical practice in gastroenterology shaped by the limited choice of drugs.

Access to treatment

Economic limitations are also a barrier to the implementation of the top-down approach in both IBD and psoriasis. The cost of biologic therapy has come to dominate the healthcare budget for both diseases in many regions of the world [131]. Variation in the cost of biologics relative to gross domestic product and systems of reimbursement has been shown to be significant determinants of the proportion of patients treated with biologics [132, 133]. Data regarding the implications of the cost of biologics on the treatment of chronic inflammatory disease in developing countries are disappointingly scant and likely conceal even more constrained access. Additionally, in clinical trials there may be overrepresentation of patients from countries where expensive therapies are not available outside of industry-sponsored studies, which has ethical implications and implications for the applicability of the data to wider populations. Some hope for mitigation of these health inequalities has come with the advent of biosimilars. Biosimilar drugs are sufficiently similar to a previously approved reference/originator biologic drugs in terms of safety, purity and efficacy such that more limited clinical trials in only one or two of the established conditions are necessary to gain regulatory approval for all indications. For the most part, biosimilars are considered interchangeable with originator drugs and evidence for their clinical application is partly extrapolated from trials of the originator. The abbreviated regulatory process results in lower research and development costs for the drug company, driving down price.

Significant cost savings are predicted to come with the process of switching from originator to biosimilars [134, 135], but evidence for the impact on accessibility is as yet lacking.

Treating patients with comorbidities

Patients with psoriasis have a higher risk to develop not only IBD but also PsA, cardiovascular disease, obesity, diabetes, depression and other comorbidities such as other immune-mediated diseases and depression; treating patients with comorbidities can be challenging [136, 137]. Along with genetic and lifestyle factors, it has been proposed that the association of psoriasis with these diseases may be explained by low-grade systemic inflammation. A number of recent studies have suggested that biologic treatment may decrease the risk of developing, in particular, cardiovascular comorbidities – however, this awaits confirmation by large prospective studies [137]. In IBD, the term 'extraintestinal manifestation' has been used to refer to inflammatory conditions thought to be driven by or dependent on the same inflammatory process as the IBD [8]. Comorbidities that are secondary to IBD such as osteoporosis also occur in IBD. However, multifocal inflammation and secondary comorbidities may overlap, a fact that is highlighted through increasing recognition of the role of inflammation in a variety of chronic diseases including obesity and the metabolic syndrome [138, 139], type 2 diabetes and [140, 141] hypertension [142]. Comorbidities may also be related to lifestyle factors such as smoking, alcohol consumption, anxiety and stress and substance misuse. Lastly, comorbidities may occur as a result of anti-inflammatory treatments such as skin cancer, dyslipidaemia, osteoporosis or lymphoma. Evidence suggests that nurse-lead programmes in comorbidity identification and management of rheumatoid arthritis patients are economically viable and acceptable to patients. Such programmes can address factors including cancer screening, blood pressure measurement, dietary advice, vaccinations, initiation of lipid-lowering or antiplatelet therapy, bone densitometry, initiation of osteoporosis therapy, physical activity, smoking and alcohol discontinuation and could be valuable if implemented in IBD or psoriasis [143, 144].

Special forms and hard-to-treat localizations

In both psoriasis and IBD, the severity of disease and response to treatment are heterogeneous as outlined above. However, in both patient groups there are also specific phenotypes that are particularly difficult to manage. Whilst most patients with plaque psoriasis respond well to biologic treatment, other forms of psoriasis (such as pustular psoriasis) represent a treatment challenge. Palmoplantar forms and nail disease can also be refractory to treatment. In certain forms of IBD such as perianal CD and fistulizing disease, remission can be difficult to attain. The management of perianal disease requires a carefully planned coordination between surgical intervention and immunosuppression. Nevertheless, in the short term, fistula closing may only be attained in 30–60% of patients [145], although with prolonged treatment, remission can be obtained in most patients.

Practice differences

Despite the many similarities in the pathogenesis and treatment of IBD and psoriasis, there are clinical challenges that are specific to each condition.

Therapeutic alternatives

In the treatment of IBD, there are 6 available biologic drugs covering 3 different molecular targets (TNF, IL-23/ IL-12 and anti-integrin therapies): for UC, the small molecule tofacitinib that inhibits the JAK-STAT pathway is also authorized; and in contrast, for psoriasis, there are around 12 available biologic drugs covering 4 therapeutic targets (TNF, IL-23/ IL-12(p40), IL-23 (p19) and IL-17) plus the small molecule phosphodiesterase-4 inhibitor apremilast. For patients with PsA, 2 further drugs (abatacept and tofacitinib) are available with 2 additional molecular targets (CD80/86 and the JAK-STAT pathway) (Tables 1 and 2). The contrasting therapeutic landscape for IBD compared with psoriasis has significantly impacted clinical practice.

Primary nonresponse to drugs

A specific challenge in the management of IBD is the phenomenon of primary nonresponse to first-line biologic drugs. For example, up to 40% of patients with CD may fail to respond to infliximab [146]. This is thought to be due to the molecular target of the therapy either not being relevant or being redundant in the inflammatory cascade in the specific individual (mechanistic failure) but may also relate to inadequate serum drug concentrations (pharmacokinetic failure). Primary nonresponse cannot be predicted, so many patients are subjected to a series

Table 1 *Drugs with European Medicines Agency (EU) or Federal Drug Agency (US) approval for either Crohn's disease (CD), ulcerative colitis (UC), psoriasis (Ps, including plaque and pustular) or psoriatic arthritis (PsA). For conditions without current approval, the current level of ongoing development is indicated (as listed on clinicalTrials.gov as of 1 June 2020). Where drug development is not currently actively pursued, the cell is blank. Relative contraindication (Rel CI) is indicated where appropriate. The number of '+' signs indicates the relative efficacy in clinical experience. However, the indication of efficacy is very approximate given that first, in general, rates of remission in IBD drug trials are much lower than those attained in psoriasis trials (i.e. 'high efficacy' has a different meaning for each condition); that secondly, the lack of head-to-head clinical trials limits the possibility to definitively define the relative efficacy of different drugs even within the same condition; and that thirdly, efficacy varies between patient groups, most notably efficacy is lower in patients who have previously not responded to or lost response to other biologic drugs. Finally, response rates differ between clinical trials where the patient population is highly selected compared with real-life experience of the use of these drugs*

Target		Drug	CD	UC	Ps	PsA
TNF-α		Infliximab	EU/US ++	EU/US ++	EU/US +++	EU/US +++
		Adalimumab	EU/US ++	EU/US ++	EU/US ++	EU/US ++
		Golimumab	–	EU/ US ++	–	EU/US +++
		Certolizumab	US ++	–	EU/US ++	EU/US ++
		Etanercept	–	–	EU/US +	EU/US +++
Anti-integrin	α4β7	Vedolizumab	EU/US +	EU/US ++	–	–
	α4β1	Natalizumab	US ++	–	–	–
IL-12/23	p40	Ustekinumab	EU/US ++	EU/US ++	EU/US +++	EU/US ++
	p19	Risankizumab	Phase 3	Phase 3	EU/US +++	Phase 3
	p19	Guselkumab	Phase 3	Phase 3	EU/US +++	EU/US +++
	p19	Tildrakizumab	–	–	EU/US ++	Phase 3
IL-17	IL-17A	Secukinumab	**Rel CI**	**Rel CI**	EU/US +++	EU/US ++
	IL-17A	Ixekizumab	**Rel CI**	**Rel CI**	EU/US +++	EU/US ++
	IL-17AR	Brodalumab	**Rel CI**	**Rel CI**	EU/US +++	–
CD80/ 86	CD80/ 86	Abatacept	–	–	–	EU/US ++
Small molecules						
JAK-STAT pathway	JAK1 & 3	Tofacitinib	–	EU/US ++	Phase 3	EU/US ++
Phosphodiesterase-4	PDE4	Apremilast	–	Phase 2	EU/US +	EU/US ++

Table 2 *Trials in adults listed on clinicalTrials.gov as of 1 June 2020, which are either active but not yet recruiting, actively recruiting or completed that have reached phase 3 development for at least one of the indications, excluding topical treatments and treatments of pruritus. Where drug development is not currently actively pursued, the cell is blank. Relative contraindication (Rel CI) is indicated where appropriate*

Target		Drug	CD	UC	Ps	PsA
JAK-STAT pathway	JAK-1	Upadacitinib	Phase 3	Phase 3	Phase 3	Phase 3
	JAK	TD-1473	Phase 2	Phase 3	-	-
	JAK-1	Filgotinib	Phase 3	Phase 3	Phase 3	Phase 3
	TYK2	BMS-986165	Phase 2	Phase 2	Phase 3	Phase 2
IL-17	IL-17A & IL-17F	Bimekizumab	**Rel CI**	**Rel CI**	Phase 3	Phase 3
	IL-17	Netakimab	**Rel CI**	**Rel CI**	Phase 3	Phase 3
IL-12/ IL-23	p40	Briakinumab	Phase 2[a]	–	Phase 3*	–
	p19	Brazikumab	Phase 3	Phase 2	-	–
	p19	Mirikizumab	Phase 3	Phase 3	Phase 3	–
Anti-integrin	MadCam1	Ontamalimab	Phase 3	Phase 3	–	–
	α4 integrin	AJM300	–	Phase 3	–	–
	β7 integrin	Etrolizumab	Phase 3	Phase 3	–	–
Sphingosine 1 phosphate receptor	S1P1	Etrasimod	Phase 2	Phase 3	–	–
	S1P1 and S1P5	Ozanimod	Phase 3	Phase 3	–	–
IL-36	IL-36R	Spesolimab	Phase 2	Phase 3	Phase 3	–
Adenosine A3 receptor	Adenosine A3 receptor	Piclidenoson	–	–	Phase 3	–

[a]Withdrawn.

of empirical trials of drugs until an effective treatment is found. Similar to the prediction of disease natural history, there is intense research activity focused on finding biomarkers that can predict drug response. Several biomarkers of lack of response to anti-TNF therapy in patients with IBD including oncostatin M [147], Il13RA2 [148], and TREM-1 [149], have been identified. None of these markers has yet been widely implemented in clinical practice; however, clinical need is driving multiple research initiatives. In contrast, primary nonresponse is unusual in psoriasis since therapies target pathways shared by most phenotypes. Furthermore, clinical phenotype can effectively guide drug choice – for example, pustular psoriasis has a distinct pathogenesis and specific drugs may be effective. Moreover, treatment choices have expanded rapidly, and today, a majority of patients with severe psoriasis achieve complete or almost complete remission. Comparing response rates and safety between drugs is not trivial since head-to-head trials are limited and comparisons are usually restricted to short-term efficacy in clinical trial settings, whilst data on long-term drug survival in real-life settings are scarce. Still, meta-analyses and daily clinical practice indicate that drugs targeting the IL-17 and IL-23 pathways have superior efficacy for psoriasis skin clearance compared with drugs targeting TNF-alpha (PMID 30289198; PMID 3158255). Still, the comorbidity profile of the individual patient plays a significant role in drug selection and the newer biologics targeting IL-23 and IL-17, even though approved for PsA, awaits positioning compared with the anti-TNFs in this respect. Indeed, PsA that affects at least 30% of patients with psoriasis remains a challenge and current therapies often do not achieve true remission.

The reason for the higher primary nonresponse rate in IBD compared with other chronic inflammatory diseases is not known but may be driven by greater molecular heterogeneity in IBD. This may be due to the huge array of antigens contained within the gut, which may drive the inflammatory response, or the unique function of the gut as a regulatory and homeostatic organ of the immune system [150]. Alternatively, failure to attain adequate serum drug concentrations may occur more frequently in IBD as discussed below.

Optimizing dose: therapeutic drug monitoring

There may be specific features of IBD that adversely affect the maintenance of consistent drug levels; for

example, loss of biologic drugs through the gut is significant in IBD, whereas serum drug concentrations may be more stable in psoriasis. With this in mind, there is increasing evidence for the benefits of proactive therapeutic drug monitoring (TDM) in IBD where serum drug levels are used to guide dose adjustment [151, 152]. Proactive TDM may also be used to guide treatment de-escalation or cessation [153-155]. TDM and the resulting higher blood concentrations of drug have been linked to improved therapeutic outcomes [156, 157] and economic benefits [158] in patients with IBD. In the management of psoriasis, TDM is employed quite seldom with dose optimization based on clinical response. Although in many chronic inflammatory diseases, the clinical imperative for intensive drug optimization is not as pressing, the adoption of the strategies developed for patients with IBD may have clinical and economic benefits. The ongoing NOR-DRUM (NORwegian DRUg Monitoring) study is taking a pan-organ approach to investigating TDM: patients with rheumatoid arthritis, PsA, spondyloarthritis, UC, CD and psoriasis will be randomized to either infliximab with TDM or standard infliximab therapy without TDM [159], and may clarify the usefulness of TDM in these different diseases. Lastly, the available assays for TDM have been largely driven by the clinical need, and as such, assays for the drugs with an IBD indication are more commonly offered in clinical practice. Future implementation of TDM more widely will need to be facilitated by better availability of assays for a wider range of drugs.

Biologic-experienced patients

In most clinical trials of biologics in IBD, patients not previously exposed to any biologic drug (biologic naïve) respond better to the trial drug than patients who have previously tried and failed a biologic (biologic failures). This appears to hold true regardless of which biologic drug the patient is exposed to first and varies according to the reason for stopping the first drug [160]. The mechanism(s) for this is(are) not known, but it is speculated that biologic failures represent a group of patients with more severe disease. Alternatively, it may be that exposure to biologic therapies induces a persistent alteration or 'priming' of the immune system, which engenders resistance to subsequent biologics. Finally, there may be patient-specific factors that lead to poorer response that act consistently across different drugs such as more rapid drug clearance leading to lower serum concentrations. In clinical trials in psoriasis, the consistently poorer response of biologic-experienced patients is not observed to the same degree, although plaque psoriasis patients with treatment failure to several biologics may represent a treatment challenge. Whether IBD represents a group of patients particularly susceptible to deleterious immunological priming through exposure to biologics, or whether the lack of this observation is accounted for by more stable drug concentrations in psoriasis patients is not known. High faecal concentrations of infliximab are observed in patients with UC in the days after infliximab infusion, and the concentration of infliximab in the stool is associated with treatment response [161]. Thus, the explanation for the difference in primary nonresponse rates between IBD and psoriasis patients may be more mundane than immunological priming or intrinsically treatment-resistant phenotypes. Drug loss (leakage) through the inflamed gut may simply render IBD patients more 'leaky' than in other chronic inflammatory disorders: loss of drug into the stool, preventing the attainment of stable therapeutic serum drug concentrations may be a problem specific to IBD.

Treatment targets

Treatment targets are defined with the aim of improving outcomes and reducing the risk of end-organ damage, which for IBD includes progression to stricture, fistula or functional gut impairment. Recently, mucosal healing defined endoscopically (but increasingly also histologically and in the future perhaps even molecularly) has become the gold standard for defining treatment success in IBD and also has been linked to improved outcomes [162, 163]. In psoriasis, the development of more efficient treatments has meant that treatment goals have become more ambitious. A 75% improvement in disease severity (PASI75), the previous gold standard, is no longer considered a sufficient treatment response, but >90% improvement, resulting in clear or almost clear skin, is often a realistic treatment goal. Since patients are frequently changed between therapies, a true baseline activity is often difficult to assess in clinical practice, and a low stable PASI score, such as PASI < 3, is today considered a more relevant target. At the same time, the patients' perspective is gaining greater attention and quality of life instruments are more frequently incorporated into treatment targets. However, it is not clear what the appropriate treatment targets for patients with multifocal inflammation such as concomitant IBD

and psoriasis are. Whether combinations of, for example, a low PASI score plus Mayo 0-1 are sufficient to describe treatment target in an patient with IBD and psoriasis or whether appropriate global treatment targets can be developed for such patients should be investigated.

Paradoxical disease

The use of biologic drugs is associated in some patients with the induction of inflammatory disease at a second site (e.g. a patient with CD may develop psoriasis during treatment with infliximab). Whilst patients with inflammatory disease intrinsically have an increased risk for developing multifocal inflammation, it would appear that new manifestations of inflammation can be drug-dependent. When a new inflammatory condition occurs during treatment with a drug usually considered as a treatment for that condition (such as infliximab), it is termed paradoxical. The prevalence of paradoxical inflammation is not certain, but it has been estimated that around 5% of patients with IBD treated with anti-TNF develop skin inflammation. This phenomenon appears to occur with variable latency after starting the anti-TNF [164]. The mechanisms for paradoxical inflammation are likely heterogeneous and are as yet ill-defined. However, there is evidence that an altered balance between cytokines may give rise to paradoxical inflammation. For example, histological analysis of anti-TNF-induced psoriasiform skin lesions in patients with IBD revealed an increased number of IFN-γ-secreting Th1 and IL-17-/IL-22-secreting Th17 lymphocytes and was associated with increased maturation of dermal plasmacytoid dendritic cells from haematopoietic progenitors [165].

Paradoxical inflammation poses a diagnostic and therapeutic challenge. Specific enquiry on the presence of skin lesions in patients newly diagnosed with IBD will define those in whom psoriasis is present before starting biologics. Similarly, screening psoriasis patients with faecal calprotectin could identify patients with concomitant IBD. In patients with IBD who are responding well to anti-TNFs and who develop paradoxical psoriasis, the decision to stop the anti-TNF can be complex. In a systematic review that identified 222 IBD patients with new psoriatic lesions during anti-TNF treatment, the anti-TNF drug was withdrawn in 86 with complete resolution in 71 cases [166]. In 87 patients, the anti-TNF was not suspended and 64 patients showed complete resolution with other treatments (e.g. topical corticosteroids). In 29 patients, the anti-TNF drug that triggered the psoriasis was replaced with another anti-TNF agent, with recurrence or aggravation of psoriatic lesions in most cases. Thus, we recommend that patients with IBD who develop skin disease during anti-TNF are referred to a dermatologist to confirm the diagnosis and a collaborative therapeutic decision-making is maintained. For milder forms of psoriasis, anti-TNF continuation with the addition of topical corticosteroids, emollients, keratolytic therapy, vitamin D analogues or phototherapy may be tried. In patients not already on immunomodulators, the addition of methotrexate or cyclosporine may be considered. Ultimately, stopping the anti-TNF is the only option for many patients, but for individuals who have attained remission of their IBD through anti-TNF treatment, this can be a difficult choice. The optimal second-line treatment will vary between individuals with many patients who are treated with anti-TNF having already proven refractory to immunomodulators. If a different biologic is indicated, then switching out of class to a biologic with efficacy in psoriasis such as ustekinumab is a logical option. Vedolizumab is also a reasonable option in patients if the psoriasis has resolved after stopping anti-TNF.

The reverse scenario (development of IBD during anti-TNF treatment for psoriasis) is less common. Paradoxical IBD (most commonly CD) has been reported in rheumatology patients receiving anti-TNF [167] or etanercept [168]. In some situations, adequate control of IBD may be attained despite anti-TNF continuation, through addition of topical therapies, 5ASA or immunomodulators. However, comparable to paradoxical psoriasis, stopping the biologic that has provoked IBD onset is often required. Given the range of available therapies for psoriasis, finding an effective alternative is less problematic, especially if the IBD regresses or is controlled with nonbiologic therapy. Small studies examining the synergistic effect of combination biologics in IBD such as vedolizumab plus infliximab have recently been reported in IBD [169-172] and in IBD in combination with spondyloarthritis [173] with some success. Dual biologic therapy may be a future option for challenging drug-induced inflammatory disease.

Conclusions

Psoriasis and IBD represent classic immune-mediated inflammatory diseases once envisioned to

follow their destined inherent course with little hope for effective not to mention curative treatment. Today, the outlook has changed dramatically, a deeper understanding of pathogenetic mechanisms hand in hand with successful drug development is now providing hope for patients, and we are even talking about changing disease course. Increased understanding of the clinical and molecular links between different chronic inflammatory conditions has developed closer collaboration between specialities in hospitals worldwide with great potential for cross-fertilization of skills and knowledge.

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Conflict of interest

C. R. H. Hedin has received speaker fees from Takeda, Ferring, AbbVie and Janssen, and consultancy fees from Pfizer. E. Sonkoly has received honoraries/speaker fees from AbbVie, Eli Lilly, UCB, Janssen, Novartis, Sanofi and LEO Pharma. M Eberhardson has received honoraria for lectures and consultancy from AbbVie, Merck (MSD), Takeda, Ferring, Orion Pharma, Otsuka, Tillotts, ITH, Novartis, Pfizer and Janssen, and received research funding from AbbVie and MSD. Eberhardson is co-founder and shareholder of EMUNE AB. Mona Ståhle has received honoraries/speaker fees from AbbVie, Eli Lilly, UCB, Janssen, Novartis and LEO Pharma.

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Correspondence: Charlotte R.H. Hedin, Division of Gastroenterology, Medical Unit Gastroenterology, Dermatovenereology and Rheumatology, Inflammation and Infection Theme, Gävlegatan 55 NB4:02, Karolinska University Hospital, 171 76 Solna, Stockholm, Sweden.
(e-mail: Charlotte.hedin@ki.se).

