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Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same?☆

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ABSTRACT

Objectives: To review the pathophysiology, co-morbidities, and therapeutic options for psoriasis, psoriatic arthritis and rheumatoid arthritis in order to further understand the similarities and differences in treatment paradigms in the management of each disease. New targets for individualized therapeutic decisions are also identified with the aim of improving therapeutic outcome and reducing toxicity.
Search strategy: Using the PubMed database, we searched literature published from 2000 to 2015 using combinations of the key words "psoriasis," "psoriatic arthritis," "rheumatoid arthritis," "pathogenesis," "immunomodulation," and "treatment."
Inclusion and exclusion criteria: This was a non-systematic review and there were no formal inclusion and exclusion criteria.
Data extraction: Abstracts identified in the search were screened for relevance and articles considered appropriate evaluated further. References within these selected articles were also screened. Information was extracted from 198 articles for inclusion in this report.
Data synthesis: There was no formal data synthesis. Articles were reviewed and summarized according to disease area (psoriasis, psoriatic arthritis, and rheumatoid arthritis).
Headline results: The pathophysiology of psoriasis, psoriatic arthritis, and rheumatoid arthritis involves chronic inflammation mediated by pro-inflammatory cytokines. Dysfunction in integrated signaling pathways affecting different constituents of the immune system result in varying clinical features in the three diseases. Co-morbidities, including cardiovascular disease, malignancies, and non-alcoholic fatty liver disease are increased. Increased understanding of the immunopathogenesis allowed development of targeted treatments; however, despite a variety of potentially predictive genetic, protein and cellular biomarkers, there is still significant unmet need in these three inflammatory disorders.

Introduction

Psoriasis is a chronic, immune-mediated, systemic disorder with a worldwide prevalence of 0.9–8.5% [1,2]. Psoriasis leads to sustained inflammation and epidermal hyperplasia, ultimately resulting in the formation and persistence of lesions, which are commonly located on the scalp, elbows, knees, umbilicus, and lumbar area [3–5]. Psoriasis impacts patients both physically and psychologically, with patients reporting reduction in physical and mental function comparable to that seen in diseases such as cancer, arthritis, heart disease, and depression [6,7], leading to marked quality of life impairment [8].

Psoriatic arthritis is a seronegative, chronic, inflammatory arthropathy often associated with psoriasis [9–11]. Prevalence estimates in the general population show marked variability, possibly due to variations in epidemiological study methodology [12]. However, using newer classification criteria, the estimated prevalence ranges from 0.16% to 0.25% [13–16]. Psoriatic arthritis may affect between 20% and 30% of patients with psoriasis [17] and is characterized by synovial hyperplasia and immune cell infiltration and expansion in both skin and synovium [9]. Patients experience pain, swelling, and joint tenderness, which produce reduced functioning in daily activities and impaired quality of life [18].

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Rheumatoid arthritis is a chronic, debilitating autoimmune disease characterized by synovial inflammation and destruction of joints. Rheumatoid arthritis affects about 0.5–1.0% of adults in developed countries [19], but 0.4% in South East Asia, and 0.37% in the Eastern Mediterranean region [20]. Prevalence rises with age and is higher in women than men [20,21]. Persistent joint inflammation and progressive joint damage eventually result in disability and decreased quality of life [18,22]; many patients have to cope with pain, depression, and fatigue [23,24].

Here we review the pathophysiology, co-morbidities, and therapeutic options for each disease in an attempt to better understand the similarities and differences in treatment paradigms in the management of each disease.

Literature search

Using the PubMed database, we reviewed literature pertaining to the role of inflammation in the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis. We used different combinations of the key words “psoriasis,” “psoriatic arthritis,” “rheumatoid arthritis,” together with “pathogenesis” or “immunomodulation,” and with or without the key word “treatment.” An example of one such combination was (psoriasis OR psoriatic arthritis OR rheumatoid arthritis) AND (pathogenesis OR immunomodulation) together with either (…OR treatment) or (…AND treatment) according to response. Our search covered the period from 2000 to 2015, but the majority of the short-listed articles were published between 2005 and 2014. Abstracts were screened for relevance; as this was not a systematic review, no formal inclusion and exclusion criteria were applied—abstracts were short-listed for full review if the studies were considered well designed and the findings relevant. Articles deemed appropriate were evaluated further and references within these selected articles were also reviewed. All types of articles, including reports of clinical trials, observational studies, literature reviews, and meta-analyses, were included if considered suitable.

Immunopathogenesis

Psoriasis, psoriatic arthritis, and rheumatoid arthritis have both similar and different clinical features. This likely reflects underlying genetic heterogeneity, with some genes implicated in pathogenesis common between the diseases, and other genes contributing to the distinct pathogenesis of each disease [25–27].

Studies suggest that each disease arises through integrated and complex signaling pathways which affect different constituents of the immune system [27–29], and have distinct roles in the pathogenesis of each disease [4,9,30,31]. It is clear that for all three diseases, both innate as well as adaptive immune responses are involved (Fig. 1A) [32–39]. Broadly, chronic inflammation mediated by T helper (Th)17 and Th1 cells is key in psoriasis [40,41], while activated T cells and macrophages are important in psoriatic arthritis [42]. In rheumatoid arthritis, T cells, B cells, and the concerted interaction of pro-inflammatory cytokines play key roles in disease pathophysiology [43].

Psoriasis

A total of 36 genes are thought to account for 22% of psoriasis heritability [44], and more than 16 genetic loci have confirmed association with psoriasis susceptibility [45]. *HLA-Cw6* on chromosome 6 is considered to be the risk variant in the *PSOR1* (MIM 177900) susceptibility locus that confers the greatest risk of early onset psoriasis [46]. The identified susceptibility genes are involved in the interleukin (IL)-23/Th17 axis of psoriasis immunopathogenesis [47].

Abundant expression of chemerin in psoriatic skin induces the infiltration of plasmacytoid dendritic cells to the dermis and epidermis; these release interferon-alpha (IFN-α), leading to the activation and maturation of myeloid dendritic cells. These cells locate to lymph nodes where they present antigens and release co-stimulatory signals and cytokines [IL-6, IL-12, IL-23, and interferon (IFN)-γ], thus inducing differentiation of naïve T cells into effector subsets and clonal expansion (Fig. 1A). T helper cells circulate back to the epidermal and dermal tissues, where a complex interaction between various cells and cytokines causes continued proliferation of keratinocytes and ongoing recruitment of T cells [38]. Cytokines implicated in the pathogenesis of psoriasis include Th1-associated [tumor necrosis factor (TNF)-α, IFN-γ and IL-2] and Th17-associated (IL-17A, IL-17F, IL-22, IL-26, and TNF-α) proteins, which are increased in serum and lesional skin [36], together with IL-23, IL-20, and IL-15 [36,48].

Psoriatic arthritis

Family studies suggest a large genetic contribution to psoriatic arthritis, particularly *HLA-Cw*0602*, *IL-23R*, and *IL-12B* [49], and the identified genes overlap with those of psoriasis. The lack of identified genetic susceptibility loci has been attributed to the lower prevalence and greater heterogeneity of psoriatic arthritis [44]. Psoriatic arthritis is thought to occur in genetically primed individuals, in which the immune response is disrupted, giving rise to immune cell infiltration as well as cytokine release [42]. Infiltrating cells, such as activated T cells and macrophages, are thought to play important roles in the induction of inflammatory and destructive processes in joint tissues, as well as inducing psoriasis in the skin [42,50].

T-cell-derived inflammatory cytokines such as IL-1β, IL-2, IL-10, IFN-γ, and TNF-α are also dominant in the synovium [42,51]. Involvement of the IL-22 and IL-23/Th17 axis has also been implicated in psoriatic arthritis [52,53]. IL-17 genes were upregulated more in skin than in synovium from paired psoriatic arthritis synovial tissue and skin samples, whereas TNF pathway upregulation was similar at both sites. Angiogenesis-related genes and IL-6 expression were upregulated in synovium but not in skin [54]. A recent review of psoriatic arthritis pathogenesis indicated that there may be four clinical phenotypes, synovial predominant, entheseal predominant, axial predominant, and mutilans, determined by genotype [55].

Rheumatoid arthritis

Genetic factors play a vital role in susceptibility to rheumatoid arthritis, with heritability between 50% and 60%. The human leukocyte antigen (HLA) locus accounts for over 30% of the overall genetic risk; non-HLA genes such as *TNF-α* have also been identified [56].

The pathogenesis of rheumatoid arthritis is characterized by inflammatory infiltrates in the synovium and synovial fluid, with a complex interplay between the adaptive and innate immune systems. Dendritic cells, mast cells, macrophages, and neutrophils have important roles in the different aspects of the disease [57]. T and B cells produce auto-antibodies and immune complexes, and secrete cytokines. In particular, T- and B-cell-associated phosphoinositide-3-kinases delta and gamma (PI3Kδ and γ), signaling molecules involved in the function of neutrophils and mast cells, have been implicated in the pathogenesis of rheumatoid arthritis.

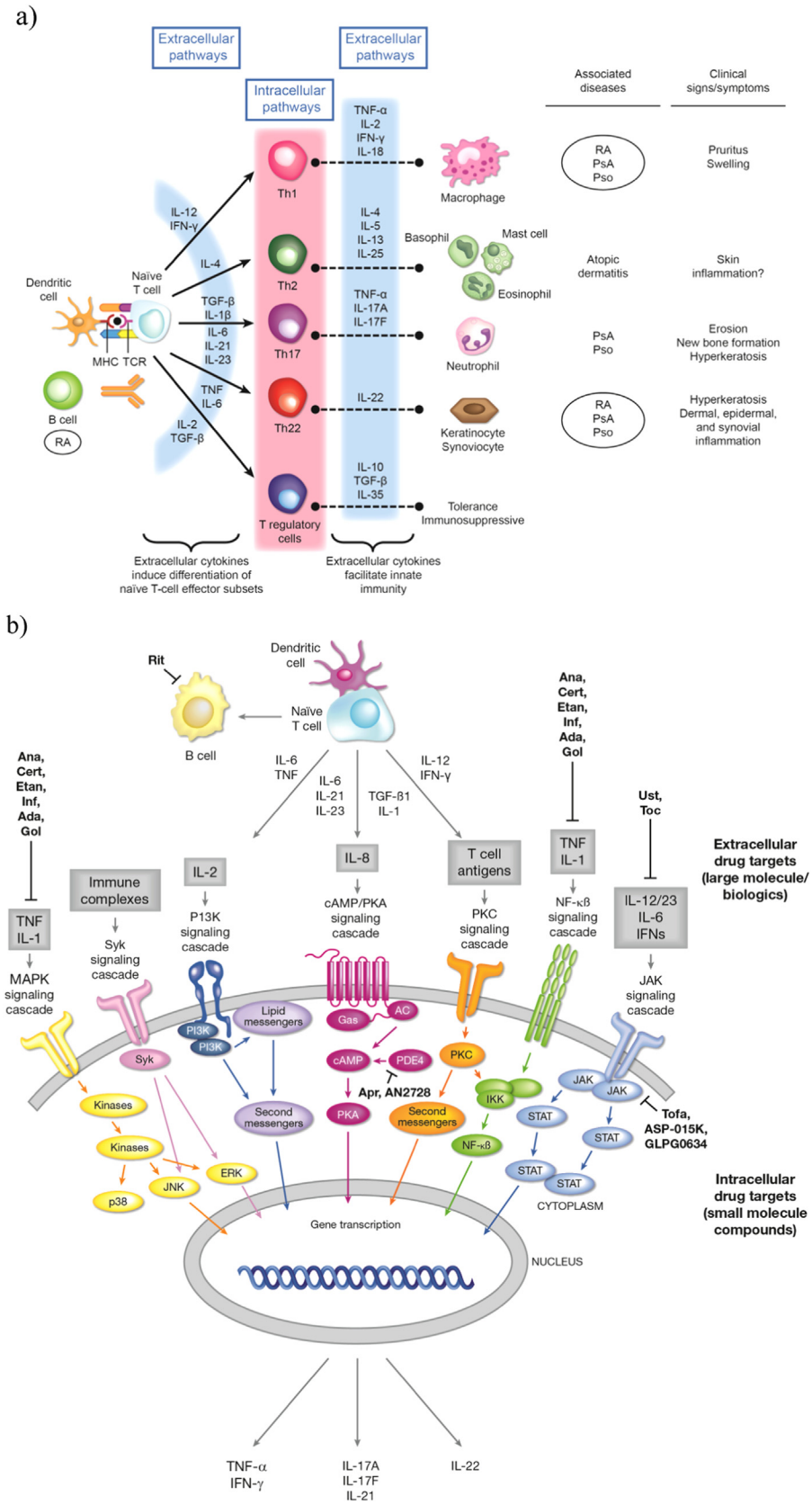


Fig. 1. (A) The cells and cytokines involved in the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis and (B) the intracellular signaling pathways involved in the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis and the targets for therapies (Reproduced of *Annual Review of Pathology*. 7, by Annual Reviews, http://www.annualreviews.org.). Ada, adalimumab; Ana, anakinra; Apr, apremilast; Cert, certolizumab; Etan, etanercept; Gol, golimumab; IFN, interferon; IL, interleukin; Inf, infliximab; MHC, major histocompatibility complex; PsA, psoriatic arthritis; Pso, psoriasis; RA, rheumatoid arthritis; Rit, rituximab; TCR, T-cell receptor; TGF, tumor growth factor; Th, T helper cells; TNF, tumor necrosis factor; Toc, tocilizumab; Tofa, tofacitinib; Ust, ustekinumab.

Co-morbidities

Immune-mediated inflammatory diseases can be associated with a variety of co-morbidities, including infections [58], malignancies [58–61], depression and anxiety [62], cardiovascular complications [63–68], non-alcoholic fatty liver disease (NAFLD) [69], and obesity [70]. Three of the most common and clinically significant co-morbidities are described below.

Cardiovascular co-morbidities

In a recent population-based cohort study, after adjustment for traditional risk factors, the risk of major adverse cardiovascular events was higher in patients with psoriasis [hazard ratio (HR) = 1.08], psoriatic arthritis (HR = 1.24), and rheumatoid arthritis (HR = 1.39) not prescribed a disease-modifying anti-rheumatic drug (DMARD), than unexposed controls [71].

Psoriasis

Psoriasis has been linked to an increased risk of adverse cardiovascular events and all-cause mortality [72]. Studies have confirmed an increased risk of myocardial infarction [73] and stroke [74]; the relative risk increased with young age and disease severity. In another study, severe psoriasis conferred an excess 6.2% absolute risk in the 10-year rate of adverse cardiac events vs. the normal population, even after adjusting for traditional cardiovascular risk factors [66]. Recent systematic reviews have confirmed the increased risk of cardiovascular morbidity in psoriasis [63,65].

Anti-inflammatory medication and TNF-α inhibitor treatment of patients with psoriasis may lower markers of cardiovascular risk including C-reactive protein, IL-6, and homocysteine levels [75]. In a recent systematic review of patients with psoriasis and/or psoriatic arthritis, the risk of cardiovascular events was significantly reduced [relative risk (RR) = 0.75] by systemic treatment [76]. Other recent reviews show a reduced risk with TNF inhibitors but not consistently with methotrexate [77,78]. Long-term ustekinumab was considered to decrease major adverse cardiovascular events in patients with psoriasis [78].

Psoriatic arthritis

Patients with psoriatic arthritis show an increased risk of myocardial infarction, angina, and hypertension compared with the general population [64,65]. As with psoriasis, in addition to the known risk factors for cardiovascular disease (diabetes and hyperlipidemia), disease severity is an important predictor of cardiovascular morbidity in patients with psoriatic arthritis.

Rheumatoid arthritis

Rheumatoid arthritis is also a risk factor for cardiovascular disease, with rates of events being highest in older patients [68,79,80]. Increased risk of atrial fibrillation, stroke and hypertension have been shown [81,82]. Systemic inflammation confers a significant additional risk for cardiovascular death among patients with rheumatoid arthritis, even after controlling for common cardiovascular co-morbidities and risk factors [83].

A systematic literature review found a significantly reduced risk of all cardiovascular events in rheumatoid arthritis after treatment with TNF inhibitors (RR = 0.7) and methotrexate (RR = 0.72) and an increased risk after corticosteroid (RR = 1.47) and non-steroidal anti-inflammatory treatment (RR = 1.18) [76].

Malignancies

Psoriasis

An increased risk of melanoma [84] and non-melanoma skin cancers (NMSC) [85,86] has been demonstrated in psoriasis patients. A recent systematic review and meta-analysis showed a small increased risk of some solid cancers associated with smoking and alcohol use in patients with psoriasis [61]. In an analysis of US claims data, patients with psoriasis had higher rates of malignancy than the general population; there was little difference in malignancy rates between patients receiving different treatments (non-biologic systemics, etanercept, other TNF-α inhibitors, and phototherapy), except for phototherapy [87].

Psoriatic arthritis

A cohort analysis of patients with psoriatic arthritis reported that 10.2% of patients developed cancer; however, this incidence did not differ from that in the general population [88]. Another study reported that malignant neoplasms were the third leading cause of death (17.0%) among patients with psoriatic arthritis after diseases of the circulatory and respiratory systems [89].

Rheumatoid arthritis

A study of cancer incidence between 1977 and 1987 in 20,699 patients with rheumatoid arthritis, reported increases in non-Hodgkin's lymphoma, Hodgkin's disease, lung cancer, and non-melanoma skin cancer, supporting findings suggesting positive associations between rheumatoid arthritis and non-Hodgkin's lymphoma, Hodgkin's disease, and lung cancer [90]. Another population-based study reported 20–50% increased risks for smoking-related cancers and a >70% increased risk for non-melanoma skin cancer [59].

Many of the malignancies are associated with psoriasis and rheumatoid arthritis rather than psoriatic arthritis, suggesting a specific disease-related risk [58]. Many are also influenced by several factors, including patients' characteristics [91], disease characteristics [92–95], and lifestyle factors [60].

Non-alcoholic fatty liver disease

Psoriasis

Several studies have found an increased incidence of NAFLD in patients with psoriasis [96]. Gisondi et al. [97] demonstrated an increased frequency of NAFLD in patients with psoriasis compared with controls matched for age, sex, and body mass index (47% vs. 28%; $p < 0.0001$), with frequency linked to severity of psoriasis. NAFLD is the most common liver disease in Indian patients with psoriasis [98].

Psoriatic arthritis

An Italian study found NAFLD to be independently associated with psoriatic arthritis in patients with psoriasis [69]; regardless of age, gender, BMI, and obesity, psoriatic arthritis was found to be a predictor of NAFLD in patients who also had psoriasis.

Rheumatoid arthritis

In the general population, NAFLD affects 10–24% of subjects, increasing to 57.5–74% in the obese [99]. An assessment of autopsy histologic liver abnormalities in patients with rheumatoid arthritis indicated that 42 of 182 cases (23%) showed fatty changes [100]. Ultrasonography has shown 23% and 15% of patients with and without rheumatoid arthritis to have NAFLD [101].

Burden and management of co-morbidities

Co-morbidities not only significantly impact daily life in the short term, but prolonged disease and associated co-morbidities could also result in cumulative impairment in many aspects of a patient's life, including their professional activities and financial status [7], and could contribute to reduced life expectancy [102].

Given the commonality of co-morbidities across all three diseases, there is a degree of overlap in their management. For example, it has been suggested that cardiovascular risk factors in patients with psoriasis should be treated as aggressively as in rheumatoid arthritis, with life-style interventions, and early statin therapy [103].

A focus is needed on awareness, screening and treatment for co-morbidities, including the potential impact on treatment choices, by all involved (rheumatologists, dermatologists, general practitioners, and patients alike), where an agreed care pathway allows optimal treatment for patients. An integrated approach has been proposed that uses algorithm-based management of co-morbidities in the dermatology setting [104].

Management: Current therapies and differential treatment algorithms

Current therapies

Historically, most treatments for psoriasis, psoriatic arthritis, and rheumatoid arthritis were developed empirically or found by chance, and consisted of effective but non-targeted agents. The early stages of these diseases are often still treated with these established agents; methotrexate is an example of an effective non-specific agent used in the treatment of psoriasis [5], early stage psoriatic arthritis [42], and rheumatoid arthritis [21,105] (Table 1).

However, our increased understanding of the immunopathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis has led to the development of targeted treatments directed at both extracellular and intracellular signaling pathways implicated in each disease.

Extracellular signaling pathways and targeted therapy

Extracellular signaling pathways transmit information between cells by activating specific receptor proteins on the cell membrane. Our increased understanding of the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis has resulted in biologic agents that specifically target key extracellular mechanisms [5,21,42,105].

In general, large molecule biologics disrupt cytokine signaling in the extracellular space by inhibiting receptor activation [35,36,38,39,116]. This type of cytokine inhibition remains central to the success of TNF blockers and biologics that block IL-6, IL-17, IL-12, and IL-23 (Fig. 1B, Table 1).

Psoriasis. In response to increased patient serum concentrations of the key cytokine, TNF-α, [36], three TNF inhibitors, etanercept, infliximab, and adalimumab, are currently used for the treatment of psoriasis [38]. Etanercept competitively inhibits interactions of TNF-α with cell-surface receptors and down-modulates Th17-activated genes, cell products, and down-stream effector molecules. Etanercept also decreases numbers of infiltrating T cells, suggesting that its efficacy may be due to a break in the cycle of dendritic-cell and T-cell activation, and pro-inflammatory mediator release [5,117,118]. In addition, etanercept may reduce IL-22 and IL-17A serum levels [119]. Infliximab reduces the cellular infiltrate in psoriatic lesions, leading to normalization of keratinocyte proliferation and differentiation [38]; it may also impair differentiation of monocyte-derived dendritic cells and activation of T cells [38,120]. Adalimumab reduces dendritic cell, macrophage, and T-cell numbers, and normalizes keratinocyte differentiation [121].

More recent therapies include ustekinumab which blocks signaling of IL-12 and IL-23 [122,123]. A systematic review of IL-12, IL-17, and IL-23 inhibitors for the treatment of moderate to severe psoriasis suggested that these biologic agents were effective [124]. The first anti-IL-17 antibody, secukinumab [115], has been

Table 1
Relationship between mechanism of action and licensed indication: current systemic therapies licensed for psoriasis, psoriatic arthritis, or rheumatoid arthritis in the European Union

Category	Molecule	Mechanism of action	Indication		
			Psoriasis	Psoriatic arthritis	Rheumatoid arthritis
Synthetic DMARDs/other	Methotrexate	Anti-metabolite [106]	X	X	X
	Leflunomide	Anti-metabolite [106]		X	X
	Corticosteroids	Direct and indirect immune mechanisms [107]		X	X
	Hydroxychloroquinine	Interference with antigen processing [108]			X
	Sulfasalazine	Anti-inflammatory and antimicrobial [109]			X
	Minocycline	Metalloproteinase inhibitor [110]			X
	Cyclosporine	T-cell-activation inhibitor [111]	X		X
	Acitretin	Activates retinoid acid receptor subtypes [112]	X		
	Fumaric acid	Modulator of intracellular glutathione [113]	X		
	Apremilast	PDE4 inhibitor [114]	X	X	
Biologics	Etanercept	Recombinant human TNF-receptor fusion protein [31]	X	X	X
	Infliximab	Humanized chimeric anti-TNF-α monoclonal antibody [31]	X	X	X
	Adalimumab	Human monoclonal anti-TNF-α antibody [31]	X	X	X
	Golimumab	TNF-α blocker [31]		X	X
	Certolizumab	TNF-α blocker [31]		X	X
	Ustekinumab	Anti-IL-12/IL-23p40 monoclonal antibody [31]	X	X	
	Anakinra	IL-1-receptor antagonist [31]			X
	Abatacept	T-cell-activation inhibitor [31]			X
	Rituximab	CD20 inhibitor [31]			X
	Tocilizumab	IL-6-receptor inhibitor [31]			X
	Secukinumab	IL-17A antagonist [115]	X	X	

CD, cluster of differentiation; DMARD, disease-modifying anti-rheumatic drug; IL, interleukin; TNF, tumor necrosis factor.

Table 2
Selected novel non-biologic agents approved in the USA and in development for the treatment of psoriasis, psoriatic arthritis, and rheumatoid arthritis

Molecule	Target/mechanism of action	Indication (FDA approved) or clinical phase		
		Psoriasis	Psoriatic arthritis	Rheumatoid arthritis
Tofacitinib	JAK-1/3 inhibitor	Phase 3	Phase 3	X
Apremilast	PDE4 inhibitor	X	X	–
Baricitinib	JAK 1/JAK 2 inhibitor	–	–	Phase 3
Ixekizumab		Phase 3	Phase 3	Phase 2
CF101	A3 adenosine receptor agonist	Phase 2/3	–	Phase 2
AN2728 (topical)	PDE4 inhibitor	Phase 2	–	–
ASP-015K	JAK inhibitor	Phase 2	–	Phase 3
ACT-128800	S1P receptor agonist	Phase 2	–	–
VB-201	TLR-2/TLR-4 antagonist	Phase 2	–	–
GLPG0634	JAK-1 inhibitor	–	–	Phase 2
CCX354-C	CCR1 antagonist	–	–	Phase 2

This table is not intended to be an exhaustive list of all novel non-biologic molecules in rheumatoid arthritis, psoriatic arthritis and psoriasis.
CCR, chemokine receptor; FDA, Food and Drug Administration; JAK, Janus kinase; PDE4, phosphodiesterase type 4; TLR, toll-like receptor improve efficacy.

approved in Europe, the USA and Japan for the treatment of moderate to severe psoriasis [125].

Psoriatic arthritis. Given the roles of T-cell activation, proliferation, and differentiation, as well as cytokine release by T cells and macrophages, in the pathogenesis of psoriatic arthritis [42], there is growing support for agents that interfere with these events.

Due to the central importance of TNF-α in the pathophysiology of psoriatic arthritis [10], the development of TNF-α inhibitors represents one of the most significant therapeutic advances in psoriatic arthritis. TNF pathway upregulation may be similar in skin and synovium [54], hence, agents have been successful in controlling all aspects of the disease [10]. Etanercept, infliximab, adalimumab, golimumab, and certolizumab are currently used for the treatment of psoriatic arthritis, often in combination with synthetic DMARDs, although a recent analysis reported similar responses to TNF inhibitors in patients with and without concomitant methotrexate [126]. A systematic literature review of drug therapies for psoriatic arthritis concluded that there was good evidence for the efficacy of anti-TNF therapy and evidence to support the use of non-steroidal anti-inflammatory drugs and synthetic DMARDs (methotrexate, cyclosporine A, sulfasalazine, and leflunomide) in this condition [127].

Other successful strategies include targeting phosphodiesterase 4, or the IL-17 or IL-12/23 pathways, although there is evidence that these approaches may be less effective than anti-TNF therapy [54,128,129]. Ustekinumab, an anti-IL-12/IL-23p40 treatment, was approved for use in psoriatic arthritis by both the FDA and the European Medicines Agency (EMA) in September 2013 [130,131]. Alternative targeted therapies include abatacept, a naïve T-cell co-stimulatory blocker that has been shown in some studies to be effective in psoriatic arthritis [132] although, to date, it has not been approved for this use.

Rheumatoid arthritis. Significant advances in the treatment of rheumatoid arthritis have been made over the past 10 years with the introduction of biologic therapies, including agents that neutralize cytokines, such as TNF-α and IL-6. Many agents,

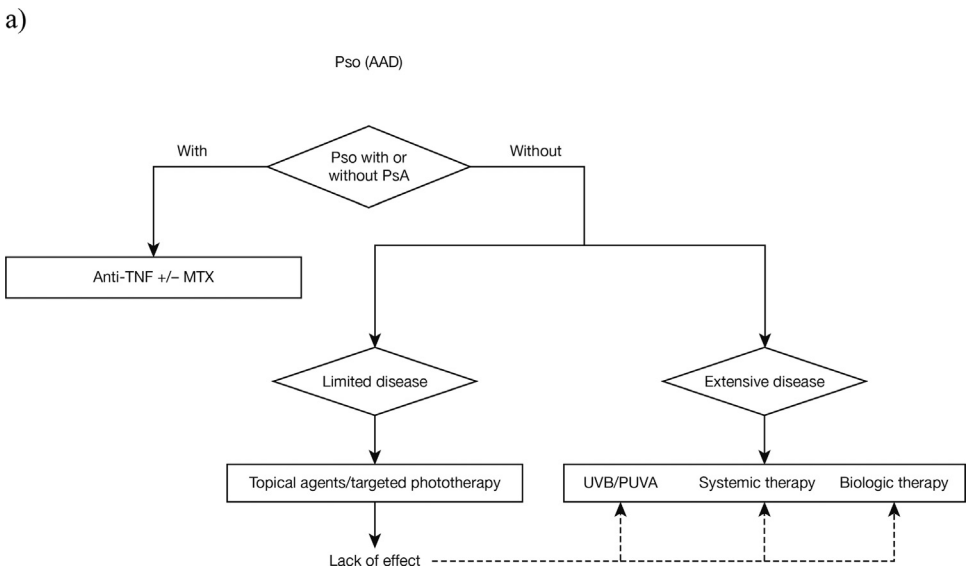


Fig. 2. Current treatment strategies for (A) psoriasis (reprinted from Menter et al. [6], copyright 2008, from Elsevier), (B) psoriatic arthritis (reproduced from Gossec et al. [154], from BMJ Publishing Group Ltd.), and (C) rheumatoid arthritis (reproduced from Singh et al. [105], from John Wiley & Sons, Inc.). AAD, American Academy of Dermatology; ACR, American College of Rheumatology; DMARD, disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquinine; LEF, leflunomide; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; Pso, psoriasis; PUVA, psoralen + ultraviolet A; RA, rheumatoid arthritis; SSZ, sulfasalazine; TNF, tumor necrosis factor; UVB, ultraviolet B. *Adverse prognostic factors: ≥ 5 active joints; or high functional impairment due to activity; or damage; or past glucocorticoid use. **The treatment target is clinical remission or, if remission is unlikely to be achievable, at least low disease activity; clinical remission is the absence of signs and symptoms.

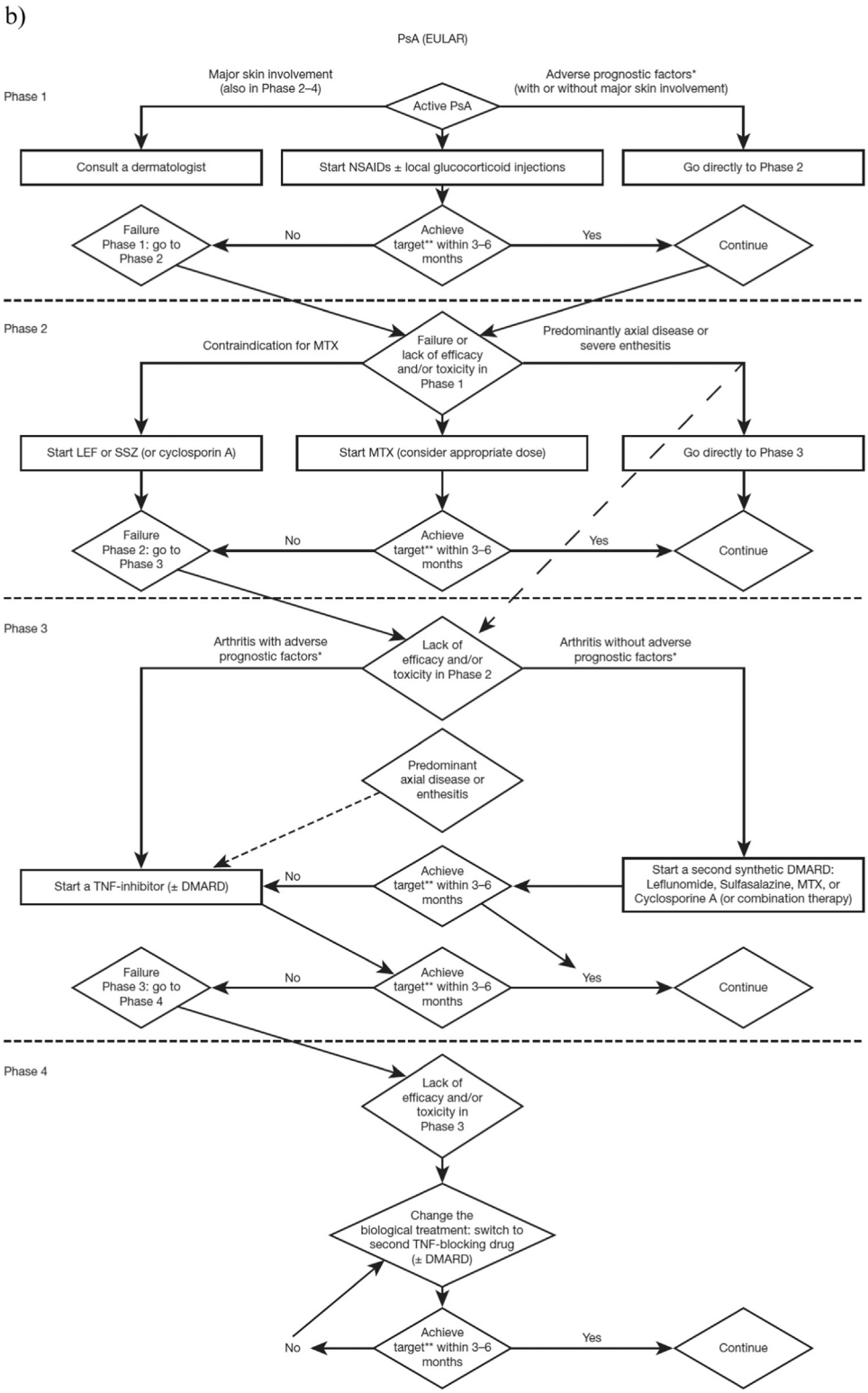


Fig. 2. Continued

including glucocorticoids and TNF inhibitors, inhibit neutrophil function which, given the important role neutrophils play in the pathogenesis of this disease [57], probably contribute to the efficacy of these agents [133,134].

Cell-targeted therapy capitalizes on the importance of both T and B cells in the pathophysiology of rheumatoid arthritis [21,105]. Rituximab, a chimeric monoclonal antibody targeting the CD20 molecule expressed on B cells, and abatacept, a CTLA4-Ig fusion molecule, are both effective in the treatment of rheumatoid arthritis [116] (Table 1).

However, limitations associated with biologic therapy include parenteral administration, cost, and they may have some undesirable side effects. As such, over the last several years, there have been intensified efforts to develop small-molecule oral agents that may represent less expensive, better tolerated, and more conveniently administered therapeutic options [135].

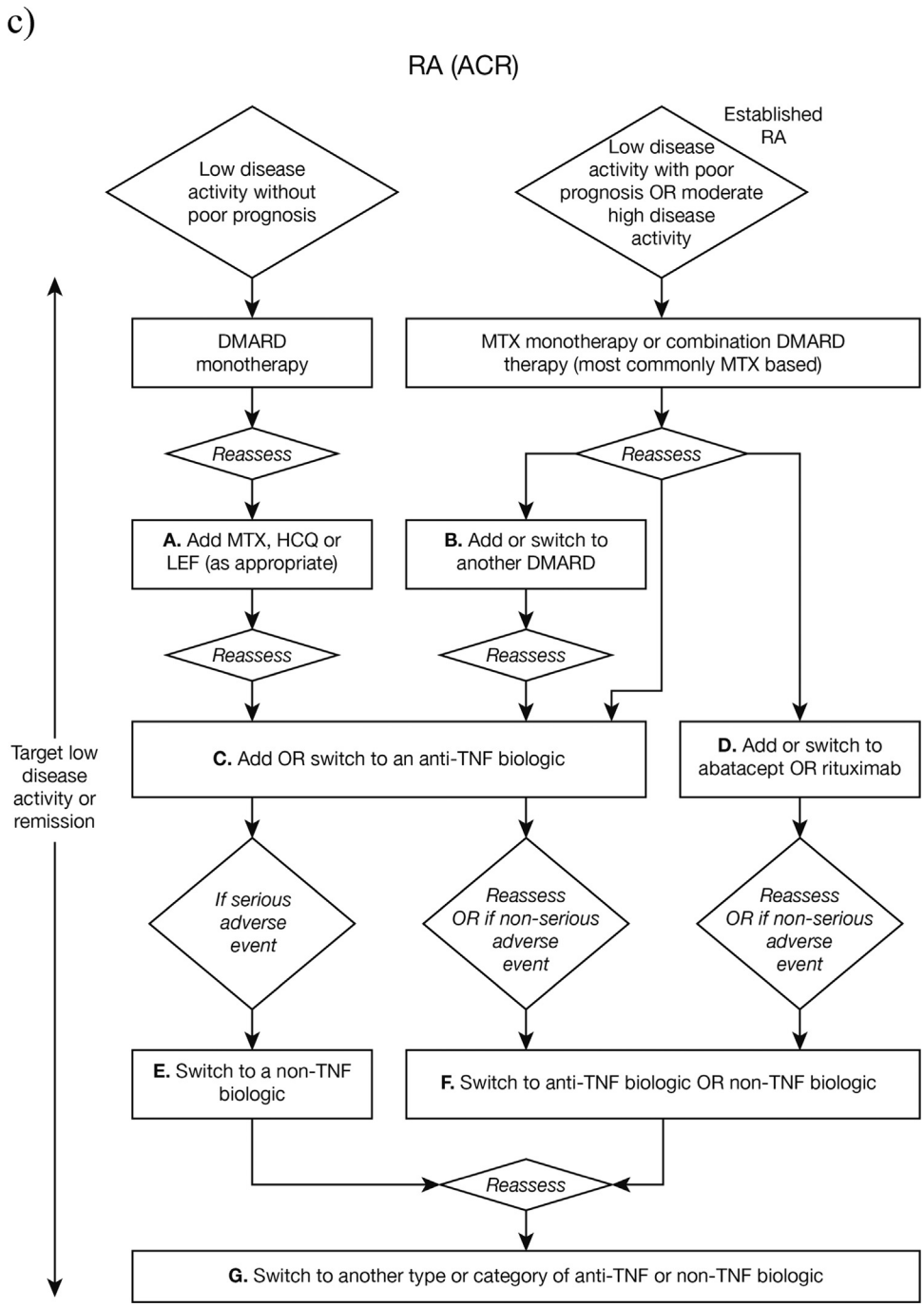


Fig. 2. Continued

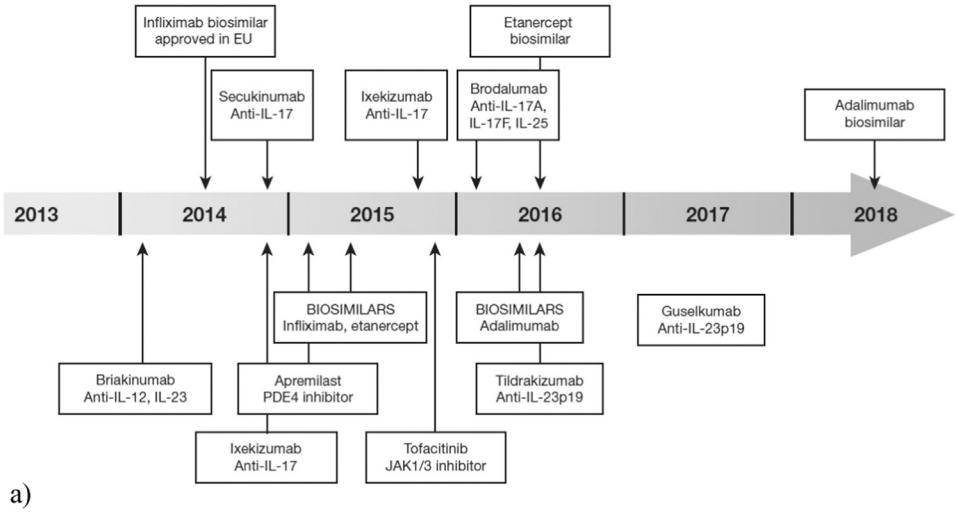
Intracellular signaling pathways and targeted therapy

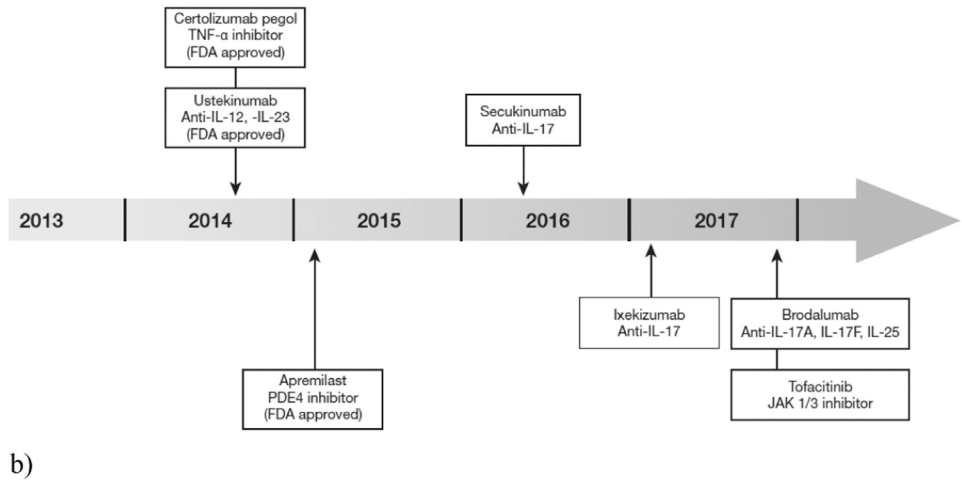
Intracellular signaling pathways transmit information to the cytoplasm and the nucleus of the cell, and thereby regulate cellular responses and gene transcription. Small molecule agents are able to target these intracellular pathways to exert their effects (Fig. 1B) [42,50,57,135-144], and include many non-biologic systemic treatments with potential in psoriasis, psoriatic arthritis, and rheumatoid arthritis (Table 2). For example, apremilast, an oral phosphodiesterase-4 inhibitor [145], has received approval for the treatment of psoriatic arthritis [146] and psoriasis [147].

The overlap in intracellular signaling cascades involved in the pathophysiology of each disease provides a rationale for the use of agents across psoriasis, psoriatic arthritis, and rheumatoid arthritis (Fig. 1B). For example, IL-2, IL-6, IFNs, and the IL-12/23 axis utilize a variety of signaling cascades currently being investigated as therapeutic targets for all three diseases. Small molecules can block intracellular enzymes important in many signaling pathways. This is exemplified by tofacitinib, an oral JAK inhibitor for the treatment of rheumatoid arthritis [148–152] that is also being investigated for psoriasis and psoriatic arthritis.

Differential treatment algorithms

The overall benefit-risk ratio is central to the utilization of any agent, and, even though some targeted immunotherapies are highly efficacious for psoriasis, psoriatic arthritis, and rheumatoid arthritis [31], variations in disease immunopathogenesis and patient demographics may mean that different mechanisms of





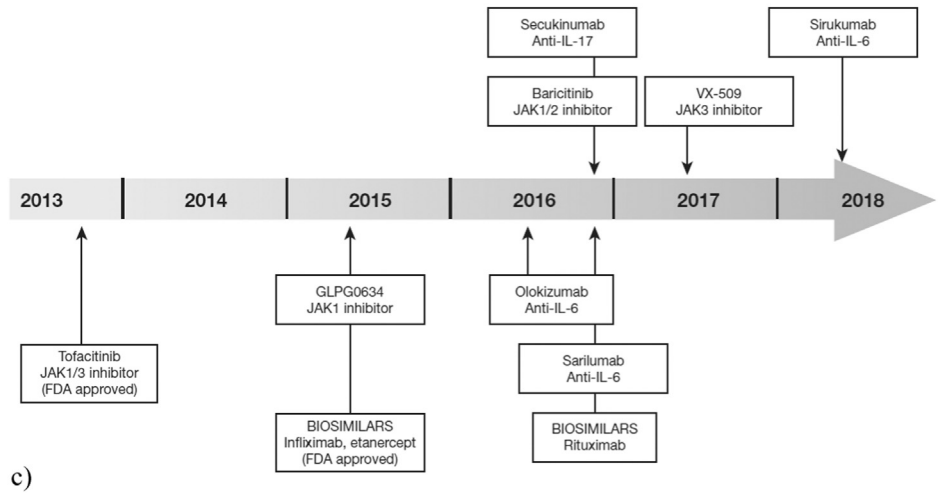


Fig. 3. Predicted innovations over the next 5 years for (A) psoriasis, (B) psoriatic arthritis, and (C) rheumatoid arthritis. IL, interleukin; JAK, Janus kinase; PDE, phosphodiesterase; TNF, tumor necrosis factor.

action may be more relevant in some diseases than others. In addition, the immunogenicity of an agent can result in the production of anti-drug antibodies, thus preventing optimum efficacy, but this may differ between diseases, as both drug- and disease-related factors can impact immunogenicity [153].

While there is much overlap in therapeutic approaches, the differences between the diseases highlighted so far mean that distinct treatment algorithms exist for psoriasis [6], psoriatic arthritis [154], and rheumatoid arthritis [105] (Fig. 2); these should continuously evolve with new clinical evidence.

Combination therapy is an especially important strategy in the clinical management of immunological diseases [155]. Methotrexate in combination with etanercept has been shown to improve efficacy compared with monotherapy in rheumatoid arthritis

[156], and observational data support the use of methotrexate in combination with TNF inhibitors in psoriatic arthritis in order to improve their effective duration of therapy [157]. Data are required comparing methotrexate with TNF inhibitors, or apremilast with combination therapy, to clearly define treatment algorithms for psoriatic arthritis. While there is evidence to suggest improved efficacy in patients with psoriasis treated with etanercept in combination with methotrexate [158], most systemic treatments in psoriasis are still currently recommended as monotherapy [159]. Recent observational studies in patients with psoriasis have also identified a loss of efficacy of TNF inhibitors over time due to anti-TNF antibodies [160–162], highlighting the need for a prospective evaluation of the combination of TNF inhibitors with methotrexate to reduce the development of anti-drug antibodies and improve efficacy.

Current thoughts, agents in development, and future perspectives

Established treatments for psoriasis, psoriatic arthritis, and rheumatoid arthritis have not fully met the needs of patients, and while there has been remarkable progress in the development of new, highly effective targeted therapies, there are still many challenges.

Our understanding of psoriasis, psoriatic arthritis, and rheumatoid arthritis reveals distinct differences between these diseases in their pathogenesis [32,34,37,38], co-morbidities, and treatment strategies [6,70,105,154,163–166]. The challenge in the management of each disease lies in the selection of treatments targeting immunopathological activity without affecting immunosurveillance. Continued investigation into the immunopathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis has resulted in a pipeline of potential new drugs for these three diseases (Fig. 3), and these agents could eventually complement the traditional systemic treatments and biological agents that are currently available [116].

Given increasing knowledge of the pathogenesis of psoriasis, psoriatic arthritis, and rheumatoid arthritis, and differing drug efficacy and safety profiles between diseases [95,167,168], it is hoped that advances in genetic analyses [28,169-180] together with the progress made in targeted therapy, may allow treatment to be tailored on the basis of an individual's genetic and immunological profile.

For this goal to be realized, one key requirement is the clear definition of disease subsets so that treatment regimens can be targeted at patients who are most likely to respond. This in turn requires the identification of genetic, protein, and cellular biomarkers that accurately predict patients' therapeutic response. Pitzalis and colleagues have recently proposed that specific pathways within synovial tissues that may be associated with therapeutic responses in patients with rheumatoid arthritis could be used as a potential clinical tool for patient treatment stratification [181]. In fact, a recent study has demonstrated that a panel of synovial-derived proteins can identify biologic responders at baseline [182].

Despite the availability of a variety of potentially predictive biomarkers (Table 3), there is still significant unmet need in these inflammatory disorders. Targeted agents have been useful in dissecting disease pathogenesis, and intracellular agents remain viable treatment options. Finally, we suggest that future research agendas should include the effects of different therapies on co-morbidities.

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All authors were involved in the conception and design of the article content, content acquisition, data interpretation, and manuscript drafting, reviewing and development. Data from this article

Table 3
Potentially predictive genetic, protein, and cellular biomarkers

Rheumatoid factor	Seropositivity may predict better response to rituximab in rheumatoid arthritis [183,184]
ACPA auto-antibodies	
Apolipoprotein A-1	May be predictive of a good response to infliximab in rheumatoid arthritis [185]
Low Type 1 IFN signature	May help to identify patients with a greater chance of responding to rituximab in rheumatoid arthritis [186]
High B-cell count during treatment	May predict a poorer response to rituximab in rheumatoid arthritis [187]
Calprotectin	Systemic and synovial fluid calprotectin levels appear to predict erosive progression and therapeutic responses in rheumatoid arthritis [188]
S100A9 protein	S100A9 is overexpressed in peripheral blood mononuclear cells and serum of rheumatoid arthritis patients who respond to methotrexate/etanercept [189]
Myeloid related protein (MRP)8/14	Changes in MRP 8/14 serum levels may predict efficacy of novel antirheumatic drugs [190]
Tartrate-resistant acid phosphatase 5b (TRACP-5b)	TRACP-5b may be a biomarker that predicts response to therapy and slowing of radiographic progression in rheumatoid arthritis [191]
Micro (mi)RNA-125b	Serum level of miR-125b may predict response to rituximab treatment in rheumatoid arthritis [192]
IL-6	Serum IL-6 in rheumatoid arthritis may estimate residual disease activity after, and predict responsiveness to, tocilizumab treatment [193]
Nitrotyrosine (NT)	NT is correlated with several biomarkers and correlates of rheumatoid disease activity and response to anti-TNF therapy [194]
TNF-α genotypes	TNFα-308GG may be a positive marker for response to TNF inhibitors in rheumatoid arthritis [195]TNFα-238GG, -857CT/TT, and -1031TT may be positive markers for response to TNF inhibitors in psoriasis [196]
IL-12B/IL-23R polymorphisms	IL-23R GG genotype may be a positive marker for response to TNF inhibitors in psoriasis [196]
HLA-Cw6	May identify patients with a greater chance of responding to ustekinumab in psoriasis [197]
IL36γ	IL36γ is expressed in psoriasis lesions only and is decreased following anti-TNFα treatment [198]
Biomarker panel including S100A8, S100A10, Ig kappa chain C fibrinogen-α and γ, haptoglobin, annexin-A1 and A2, vitronectin, alpha-1 acid glycoprotein	Multiplexed protein assay may predict response to treatment in psoriatic arthritis [182]

ACPA, anti-citrullinated protein antibodies; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

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