Psoriatic arthritis is a debilitating condition, which affects approximately one-quarter of psoriasis patients. Recent findings have furthered our understanding of the complex pathophysiology of PsA. There have been major advances in the identification of genes associated with joint involvement but not with cutaneous disease alone. The elucidation of key immunologic pathways has allowed the development of novel targeted therapies that are in the research pipeline. Currently, good screening tests and biomarkers to diagnose early PsA and to guide therapy are limited. In this paper, we present recent findings with regard to the immunopathogenesis and genetics of PsA, biomarkers, and screening tools and review the targeted therapies currently in clinical trials.

1. Introduction

Psoriatic arthritis (PsA) is an inflammatory arthropathy, which is associated with psoriasis in approximately 25% of patients. It is characterized by stiffness, pain, swelling, and tenderness of the joints as well as the surrounding ligaments and tendons [1, 2]. It affects men and women equally and typically presents at the age of 30 to 50 years [2]. Cutaneous disease usually precedes the onset of PsA by an average of 10 years in the majority of patients but 14–21% of patients with PsA develop symptoms of arthritis prior to the development of skin disease [2]. Psoriatic arthritis is classified as a seronegative spondyloarthritis due to the potential axial involvement, the contribution of enthesitis to its pathogenesis, and increased association with HLA-B27 [3]. The presentation is variable and can range from a mild, nondestructive arthritis to a severe, debilitating, erosive arthropathy.

There are multiple clinical subsets as defined by Moll and Wright: monoarthritis of the large joints, distal interphalangeal arthritis, spondyloarthropathy, or a symmetrical deforming polyarthropathy much akin to that of rheumatoid arthritis. Left untreated, a proportion of patients may develop persistent inflammation with deforming progressive joint damage which leads to severe physical limitation and disability [3]. In many patients articular patterns change or overlap in time [2]. Enthesitis may occur at any site, but more commonly at the insertion sites of the plantar fascia, the Achilles tendons, and ligamentous attachments to the ribs, spine, and pelvis [4]. Dactylitis, an important feature of PsA, is a combination of enthesitis of the tendons and ligaments and synovitis involving all joints in the digit. The severity of the skin and joint disease frequently do not correlate with each other. Although in the past it was always thought that the presence of nail psoriasis correlated with the development of psoriatic arthritis, more recent evidence does not support this [5]. Ocular manifestations of PsA include conjunctivitis, iritis, and urethritis. Radiographic characteristics of PsA include the development of erosions, the presence of pencil-in-cup deformity, arthritis mutilans, spur formation, nonmarginal asymmetric syndesmophytes, and asymmetric sacroiliitis.

In the past decade, considerable progress has been made in further elucidating the immunologic and genetic basis of PsA, and defining its clinical and epidemiologic characteristics. More importantly, there have been significant advances in the development of more targeted systemic and biologic treatments for PsA. This update review advances in the field of psoriatic arthritis in the past decade and discusses the future direction of PsA research and therapy.
2. Advances in Epidemiology

It is imperative to diagnose psoriatic arthritis at its first onset because early diagnosis and treatment may reduce irreversible joint damage. Patients with PsA who were started on etanercept within two years of disease onset had a more significant improvement in pain assessments than those who had PsA for more than two years prior to commencing etanercept [6]. Additionally, the SwePsA registry found that the early diagnosis of psoriatic arthritis was associated with lower joint disease activity at the 5-year follow-up time point [7]. In this study, male gender, axial disease, preserved function at diagnosis and lower baseline health assessment questionnaire scores also portended a better prognosis. Surprisingly, it was also shown that male gender was a predictor of more rapid radiological progression despite a better clinical outcome [8].

3. Advances in Screening and Biomarkers of Disease Activity

Early detection of PsA is difficult in the absence of a validated screening test or biomarkers of disease activity. The Classification of Psoriatic Arthritis (CASPAR) system is the most widely used criteria for diagnosis. Unfortunately, there are many patients with undiagnosed PsA [2]. For example, in one study, 29% of the psoriatic patients in dermatology clinics in Dublin had undiagnosed PsA, while in another study more than one-third of patients seen in 34 dermatology centers in Europe and North America had undiagnosed PsA [9, 10]. As a result, screening for and early detection of psoriatic arthritis must improve.

Korotaeva et al. showed that early detection of PsA can be accomplished by the combination of a clinical exam and magnetic resonance imaging (MRI), and that MRI may be superior in diagnosing tenosynovitis [11]. One study showed that patients with active PsA have elevated total serum IgG and more cell surface bound IgG, making Fc receptors possible biomarkers of disease activity [12]. Interleukin-23 (IL-23) serum concentration has also been evaluated as a possible biomarker of disease activity, but no correlation with disease activity was found [13]. Another study compared the serum levels of various potential biomarkers and the presence of scalp and nail involvement, in patients with cutaneous disease alone and patients with joint involvement [14]. It was shown that a tool incorporating high sensitivity C reactive protein, osteoprotegerin (OPG), matrix metalloproteinase 3 (MMP-3), and the ratio of C-propeptide of Type II collagen (CPII) to collagen fragment neoepitopes Col2-3/4(long mono) (C2C), in association with the presence of nail and scalp psoriasis could be helpful in screening for PsA [14]. Further studies to determine the best screening method are warranted, as early diagnosis significantly decreases morbidity and increases the quality of life in patients with PsA.

Currently, there is no validated disease activity score for psoriatic arthritis. The two most promising measures are the modified composite psoriatic disease activity index (mCPDAI) and the arithmetic mean desirability function (AMDF). The mCPDAI is a composite score of 4 domains: joints, skin, dactylitis, and enthesis. The AMDF is calculated from the cutaneous involvement, joint, and global VAS assessment. Both of these appear to correlate best with disease activity [9].

4. Comorbidities

It is now well known that psoriatic patients are at higher risk for the metabolic syndrome and thus have a larger waist circumference. It was recently shown, however, that there is no correlation between a larger waist circumference and more severe PsA [15, 16]. Interestingly, a prospective study of 135 obese and 135 nonobese PsA patients starting tumor necrosis factor-alpha (TNF-α) inhibitors showed that obese patients were less likely to achieve minimal disease activity (MDA) (hazard ratio: 4.90, 95% CI: 3.04–7.87, P < 0.001). Of those who achieved MDA, obese patients were more likely to relapse at 24 months [17].

Another prospective study among 138 obese PsA patients commencing TNF-α inhibitors on a self-managed diet or hypocaloric diet showed that the adherence to a hypocaloric, fiber-enriched diet associated greater likelihood of achieving MDA [18]. Studies have shown that patients with psoriasis, gout, and rheumatoid arthritis have an increased risk of acute myocardial infarction [19]. Using the Kaiser Permanente healthcare database in California, a retrospective cohort study of 24,081 psoriasis and PsA patients examined the effect of TNF-α inhibitors on the incidence of myocardial infarction [20]. A multivariable analysis was performed to control for cardiovascular risk factors. Patients receiving TNF-α inhibitors had a 48% reduction in the risk of myocardial infarction (P = 0.0062) [20]. The presence joint involvement increased the risk of myocardial infarction by 42% [20].

5. Advances in Understanding the Immunologic Pathogenesis of Psoriatic Arthritis

Current literature suggests that both acquired and innate immunity are responsible for the development of PsA [21, 22]. Until recently, psoriasis and PsA were thought to be predominately Th1-cell mediated diseases based on the large number of interferon-gamma producing cells found in cutaneous eruptions [23]. Recent studies have proposed that the T helper 17 (TH17) cell plays a more pivotal role in the pathology of psoriasis and PsA. T helper 17 cells are a subset of helper T cells and differ functionally from Th1 and Th2 helper cells [23]. TH17 cells induce acquired immune responses against microbes and produce interleukin (IL) 17A, IL-17F, IL-21, and IL-22 [24].

Tumor necrosis factor-alpha, interferon gamma, interferon-alpha, IL-6, and IL-1beta induce the secretion of IL-12 and IL-23 by myeloid dendritic cells which cause the differentiation of TH-1 and TH17 cells, respectively, [25]. TH17 cells then produce IL-17 which induces the production of proinflammatory cytokines and angiogenic factors [25]. It also commits naive T cells to the TH17 lineage thus creating a positive feedback loop for Th17 inflammation.
osteoprotegerin is downregulated [30]. RANKL is also markedly upregulated and its natural antagonist into activated osteoclasts [22]. In psoriatic synovial tissues, expressed in the fibroblastoid cells of the synovial lining and the receptor activator of nuclear factor kappa B (RANKL) which is required for the receptor activator of nuclear factor κB ligand (RANKL) to trigger the differentiation of osteoclast precursor cells into activated osteoclasts [22]. In psoriatic synovial tissues, RANKL is markedly upregulated and its natural antagonist osteoprotegerin is downregulated [30]. Tumor necrosis factor-alpha also induces the expression of receptor activator of nuclear factor κB (RANK) which is required for the receptor activator of nuclear factor κB ligand (RANKL) to trigger the differentiation of osteoclast precursor cells into activated osteoclasts [22]. In psoriatic synovial tissues, RANKL is markedly upregulated and its natural antagonist osteoprotegerin is downregulated [30]. RANKL is also expressed in the fibroblastoid cells of the synovial lining and by the T cells infiltrating the synovium, providing an additional stimulus to activate osteoclasts [30]. This upregulation of activated osteoclasts causes bone resorption which leads to the manifestations of psoriatic arthritis [30].

6. Genetics

It was once thought that psoriasis and psoriatic arthritis were a continuum resulting from key genetic polymorphism. Recent studies have shown that there are distinct genetic differences between the two diseases. Population-based studies have shown that the heritability of PsA is 3–5 times higher than that of psoriasis [22, 31]. Overall, the gene MICA*002 is more specific to PsA than psoriasis and certain genes have been found to be more frequently associated with specific types of PsA [32]. For example, HLA-B38 and HLA-B39 are more frequent in peripheral PsA and HLA-B27 is more frequently seen in PsA with spondylitis [32]. Psoriatic arthritis patients with HLA-B27 or DQB1*02 were shown to have an increased risk of developing arthritis mutilans, the most severe form of psoriatic arthritis [33]. Additionally, HLA-B*39, HLA-B*27, and HLA-A*02 and the KIR gene KIR3DS1 were found to be independently associated with the increased progression of peripheral joint damage, whereas the alleles DQB1*0604, C*04, and B*50 were associated with decreases progression [34].

The IL-13 locus associates with PsA, but not psoriasis [22]. Bowes et al. found two IL-13 single nucleotide polymorphisms (SNPs), rs1800925, and rs20541 with the major allele, rs1800925, conferring disease susceptibility [33]. This association has been reported previously but contradicts the findings of Nair et al. who showed that IL-13 has a significant association with both psoriasis and PsA [36]. Another SNP, rs104 8455, at the class I region of MHC just 34.7 kb upstream from HLA-C has also been linked to psoriatic arthritis [37]. Additionally, genomewide association study (GWAS) data has shown that the rs10782001 variant of FBXL9, a gene in the NFkB network, is more frequent in PsA and the effect size of the TRAF3 interacting protein (TRAF3IP2) in the Th17 pathway, to be mildly higher in PsA [38, 39]. The GWAS has also identified variants in several genes in the NFkB signaling network, including TNFAIP3, TNIP1, NFKBIA, REL, and NOS2, which have been implicated in PsA [40–43]. VEGF gene polymorphisms have also been found to be associated with different psoriatic arthritis phenotypes. For example, the peripheral joint involvement of psoriatic arthritis was associated with the VEGF polymorphism C(-2578)A [44].

7. Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) help with symptomatic relief, but they do not alter the disease course or prevent disease progression. Intra-articular steroid injections can be used for symptomatic relief. In psoriatic arthritis, dramatic flares in skin disease have been reported with corticosteroid taper; therefore, systemic corticosteroids ideally should be avoided in this patient population [3]. Physical therapy may also be helpful in symptomatic relief. Disease modifying anti-rheumatic drugs (DMARDs) are the mainstay of treatment for patients suffering from PsA. Traditional oral agents include methotrexate, sulfasalazine, cyclosporine and leflunomide. The TNF-α inhibitors include etanercept, infliximab, adalimumab, and golimumab. Currently, the most effective class of therapeutic agents for treating PsA is the TNF-α inhibitors; however, these drugs show a 30 to 40% primary failure rate in both randomized clinical trials and registry-based longitudinal studies [45–47].

A recent phase III trial of ustekinumab, an IL-12/23 inhibitor, for PsA showed ACR-20 responses of 42.4% for ustekinumab 45 mg weekly and 49.5% for ustekinumab 90 mg weekly compared to 22.8% for placebo at 24 weeks [48]. Even though an ACR-20 of nearly 50% was obtained with 90 mg of ustekinumab weekly; etanercept produces an ACR20 of 39% at 24 weeks, adalimumab an ACR20 of 58% at 12 weeks which is maintained to 24 weeks, and infliximab an ACR20 of 58% at week 14 which was maintained to 24 weeks [49–51].

Secukinumab (AIN457, Novartis) a fully human anti-interleukin-17A antibody was evaluated in 18 patients with psoriatic arthritis. Although there was some improvement in clinical scores, the primary endpoint of the proportion of ACR20 responders at week 6 was not met with 39% and 23% of patients treated with secukinumab versus placebo achieving an ACR-20 response (P = 0.27) [52]. The safety profile of secukinumab was favorable and the most common adverse events were headache and gastrointestinal disturbance [52]. It is currently undergoing a phase III trial which is evaluating the efficacy and safety in PsA whom have not responded to current therapies. (http://www.clinicaltrials.gov/, NCT01169844). There is also a trial underway evaluating its long-term safety and efficacy up to two years in patients with active PsA. (http://www.clinicaltrials.gov/, NCT01392326).

Apremilast (CC-10004, Celgene) is an oral small molecule inhibitor of phosphodiesterase type 4 (PDE4), which results in decreased production of IL-2, IL-12, IFN gamma, TNF-α, leukotrienes, and decreased activity of nitric oxide.
Psoriatic arthritis is an inflammatory arthritis with a number of clinical patterns. Currently there are no validated screening serological methods to aid in early clinical diagnosis. Psoriatic arthritis is associated with different degrees of disability and an increased mortality risk especially when there is a delay in diagnosis. There are distinct genetic differences between psoriatic patients who develop PsA and those who remain free of joint involvement. This likely produces differences in the microenvironment of the skin and synovial tissues where inflammatory mediators are not identical. Treatment options include symptomatic as well as disease modifying agents either singly or in combination. Therapeutic agents beneficial for the cutaneous manifestations of psoriasis may not necessarily be equally efficacious for PsA and vice versa. However, even with the most effective agents there are still a significant percentage of treatment failures, creating the need for the further development of more effective and safer treatment options. Several medications are currently undergoing clinical trials and are showing promising results. Patients with PsA should be diagnosed early and treated promptly and aggressively in order to prevent joint destruction and poor clinical outcomes.

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References

[1] A. Gottlieb, N. J. Korman, K. B. Gordon et al., “Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics,” Journal of the American Academy of Dermatology, vol. 58, no. 5, pp. 851–864, 2008.
[2] D. D. Gladman, C. Antoni, P. Mease, D. O. Clegg, and O. Nash, “Psoriatic arthritis: epidemiology, clinical features, course, and outcome,” Annals of the Rheumatic Diseases, vol. 64, supplement 2, pp. ii14–ii17, 2005.
[3] J. H. Klippel, Primer on the Rheumatic Diseases, Springer, New York, NY, USA, 13th edition, 2008.
[4] E. Naredo, I. Möller, E. de Miguel et al., “High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study,” Rheumatology, vol. 50, no. 10, pp. 1838–1848, 2011.
[5] K. M. Wittkowski, C. Leonardi, A. Gottlieb et al., “Clinical symptoms of skin, nails, and joints manifest independently in patients with concomitant psoriasis and psoriatic arthritis,” PLoS ONE, vol. 6, no. 6, Article ID e20279, 2011.
[6] B. W. Kirkham, W. Li, R. Boggs, H. Nab, and M. Tarallo, “Early treatment of psoriatic arthritis is associated with improved outcomes: findings from the etanercept PESTA,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[7] E. Theander, T. Husmark, G. M. Alenius et al., “The Swedish early psoriatic arthritis (SwePsA) registry. 5-year follow-up: worse outcomes for women compared to men,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[8] M. Geijer et al., “The Swedish early psoriatic arthritis (SwePsA) registry 5 year follow up: slow radiographic progression of bone destruction in the hands without correlation to clinical disease activity,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[9] M. Haroon et al., “High prevalence of articular involvement in patients with severe psoriasis with poor performance of screening questionnaires,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[10] P. J. Mease et al., “The prevalence of rheumatologist-diagnosed psoriatic arthritis in psoriasis patients in European/North American dermatology clinics: results of PREPARE study,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[11] T. Korotaeva et al., “Clinical examination versus magnetic resonance imaging of the hand and foot: its usefulness in early detection of psoriatic arthritis among patients with psoriasis,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[12] J. Matt et al., “Fc gamma receptors in active psoriatic arthritis,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[13] H. Przepiera-Bedzak et al., “Serum IL-23 does not correlate with disease activity in psoriatic arthritis and SAPHO syndrome,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.
[14] V. Chandran et al., “A screening tool that includes key clinical features and biomarkers discriminates patients with psoriatic arthritis from those with psoriasis without psoriatic arthritis,”
in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.

[15] D. M. Sommer, S. Jenisch, M. Suchan, E. Christophers, and M. Weichenthal, “Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis,” Archives of Dermatological Research, vol. 298, no. 7, pp. 321–328, 2006.

[16] N. Kogan et al., “Psoriasis and psoriatic arthritis: large waist circumference and severity assessment,” in Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis, Stockholm, Sweden, June 2012.

[17] R. P. Di Minno, S. Iervolino, A. Lupoli, P. Russoillo, R. Bottiglieri, and G. Scarpa, “Obesity and the prediction of the minimal disease activity, a prospective study in psoriatic arthritis patients,” Annals of the Rheumatic Diseases, vol. 71, supplement 3, p. 145, 2012.

[18] S. I. Di Minno, R. Peluso, A. Lupoli, P. Russoillo, R. Bottiglieri, and G. Scarpa, “Weight loss and induction of minimal disease activity in psoriatic patients starting TNF-alpha blockers treatment,” Annals of the Rheumatic Diseases, vol. 71, supplement 3, p. 109, 2012.

[19] O. Schieir, O. Tosevski, and E. M. Cedomir Badley, “Risk of tumor necrosis factor alpha attenuates collagen-induced arthritis in rats,” Arthritis & Rheumatism, vol. 58, no. 5, pp. 423–431, 2008.

[20] J. Wu, A. Shen, A. Fisher et al., “The effect of tumor necrosis factor-alpha inhibitors on the risk of myocardial infarction in patients with psoriasis,” in Proceedings of the Annual Meeting of the American Academy of Dermatology, Louisiana State University, New Orleans, La, USA, 2011.

[21] C. T. Ritchlin, “From skin to bone: translational perspectives on psoriatic disease,” Journal of Rheumatology, vol. 35, no. 7, pp. 1434–1437, 2008.

[22] D. D. O’Reilly and P. Rahman, “Genetics of susceptibility and treatment response in psoriatic arthritis,” Nature Reviews Rheumatology, vol. 7, no. 12, pp. 718–732, 2011.

[23] S. Maeda, Y. Hayami, T. Naniwa, and R. Ueda, “The Th17/IL-23 axis and natural immunity in psoriatic arthritis,” International Journal of Rheumatology, vol. 2012, Article ID 539683, 8 pages, 2012.

[24] S. C. Liang, X. Y. Tan, D. P. Luxenberg et al., “Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides,” Journal of Experimental Medicine, vol. 203, no. 10, pp. 2271–2279, 2006.

[25] C. Ryan, A. Abramson, M. Patel, and A. Menter, “Current investigational drugs in psoriasis,” Expert Opinion on Investigational Drugs, vol. 21, no. 4, pp. 473–487, 2012.

[26] A. W. R. van Kuijk, P. Reinders-Blankert, T. J. M. Smeets, B. A. C. Dijkmans, and P. P. Tak, “Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment,” Annals of the Rheumatic Diseases, vol. 65, no. 12, pp. 1551–1557, 2006.

[27] T. Yago, Y. Nanke, M. Kawamoto et al., “IL-23 induces human osteoclastogenesis via IL-17 in vitro, and anti-IL-23 antibody attenuates collagen-induced arthritis in rats,” Arthritis Research and Therapy, vol. 9, no. 5, article R96, 2007.

[28] L. van Baarsen, M. C. Lebre, D. van der Coelen, D. M. Gerrag, and P. P. Tak, “Expression levels of interleukin-17A, interleukin-17F and their receptors in synovium of patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis: a target validation study,” Arthritis & Rheumatism, vol. 71, no. 1, article A6, 2012.

[29] M. S. Hayden and S. Ghosh, “NF-κB in immunobiology,” Cell Research, vol. 21, no. 2, pp. 223–244, 2011.
[45] A. A. Saad, D. M. Ashcroft, K. D. Watson et al., “Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British society for rheumatology biologics register,” *Rheumatology*, vol. 49, no. 4, pp. 697–705, 2010.

[46] L. E. Kristensen, A. Gülfe, T. Saxne, and P. Geborek, “Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish arthritis treatment group register,” *Annals of the Rheumatic Diseases*, vol. 67, no. 3, pp. 364–369, 2008.

[47] A. A. Saad, D. P. M. Symmons, P. R. Noyce, and D. M. Ashcroft, “Risks and benefits of tumor necrosis factor-α inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials,” *Journal of Rheumatology*, vol. 35, no. 5, pp. 883–890, 2008.

[48] I. McInnes, A. Kavanaugh, A. B. Gottlieb et al., “Ustekinumab in patients with active psoriatic arthritis: results of the phase III, multicenter, double-blind, placebo-controlled PSUMMIT I study,” in *Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis*, Stockholm, Sweden, June 2012.

[49] P. J. Mease, A. J. Kivitz, F. X. Burch et al., “Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression,” *Arthritis & Rheumatism*, vol. 50, no. 7, pp. 2264–2272, 2004.

[50] P. J. Mease, D. D. Gladman, C. T. Ritchlin et al., “Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial,” *Arthritis & Rheumatism*, vol. 52, no. 10, pp. 3279–3289, 2005.

[51] C. Antoni, G. G. Krueger, K. De Vlam et al., “Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial,” *Annals of the Rheumatic Diseases*, vol. 64, no. 8, pp. 1150–1157, 2005.

[52] I. McInnes et al., “Secukinumab, a fully human anti-interleukin-17A antibody, improves signs and symptoms of psoriatic arthritis: a 24-week, double-blind, placebo-controlled, multicenter trial,” in *Proceedings of the 3rd World Congress of Psoriasis and Psoriatic Arthritis*, Stockholm, Sweden, June 2012.

[53] G. Schett, J. Wollenhaupt, K. Papp et al., “Oral apremilast in the treatment of active psoriatic arthritis: results of a multi-center, randomized, double-blind, placebo-controlled study,” *Arthritis & Rheumatism*, vol. 64, no. 10, pp. 3156–3167, 2012.

[54] http://www.Clinicaltrials.Gov/ct2/results?Term=psoriasis.