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New Frontiers in Psoriatic Disease Research, Part II: Comorbidities and Targeted Therapies

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Abstract

While psoriasis and psoriatic arthritis have been classically considered to be diseases of the skin and joints, respectively, emerging evidence suggests that a combination of innate and environmental factors creates widespread immune dysfunction, affecting multiple organ systems. A greater understanding of the pathogenesis of psoriasis and the systemic effects of psoriatic inflammation has allowed for the development of new, more effective treatments. The second of this two-part review series examines comorbidities associated with psoriasis and psoriatic arthritis as well as the most recent advances in targeted systemic therapies for these conditions.

Introduction

Novel techniques in medical imaging and molecular biology are revealing how psoriatic disease affects the whole body and how changes in lifestyle can, in turn, influence the course of the disease. These advances have fundamentally changed the way we manage psoriasis and psoriatic arthritis (PsA), leading to more targeted therapies and integrated treatment approaches. The second portion of this two-part review series will examine the

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links between psoriasis, cardiometabolic disease, psychiatric comorbidities, as well as the latest in clinical research for targeted systemic therapies.

Metabolic comorbidities of psoriasis and PsA

Psoriasis is associated with an increased risk of both metabolic syndrome and type 2 diabetes (DM2). Patients with psoriasis have an increased incidence of DM2 even when controlling for body mass index (BMI), smoking, cardiovascular disease, hypertension, and hyperlipidemia (Azfar et al., 2012, Brauchli et al., 2008, Khalid et al., 2013). Furthermore, large, prospective cohort studies have shown that the risk of DM2 is correlated in a dose dependent manner with psoriasis body surface area (Noe et al., 2018) and with the presence of PsA (Noe et al., 2018, Wan et al., 2018). Recently a causal relationship and shared genetic loci was demonstrated between psoriasis and DM2, through overlapping NF-κB signaling mechanisms (Patrick et al., 2020).

The chronic inflammatory states of psoriasis, metabolic syndrome, and DM2 have many similarities, including a predominance of Th1 and Th17 cells and pro-inflammatory cytokines TNF-α and IL-6 (Davidovici et al., 2010). TNF-α inhibits the activity of insulin receptors and reduces the expression of the glucose transporter, GLUT4, leading to insulin resistance (Gupta et al., 2007, Uysal et al., 1997). Additionally, psoriasis, obesity, and hyperinsulinemic states are characterized by adipokine profiles that are high in leptin and resistin, and low in adiponectin (Kyriakou et al., 2017). Adiponectin, a cardioprotective regulator of insulin sensitivity and immune responses, also has an anti-inflammatory effect in the skin and has been shown to suppress IL-17 production by human $CD4^+$ and $CD8^+$ cells and TNF-α and IL-6 by human keratinocytes *in vitro* (Shibata et al., 2011, Shibata et al., 2015). Furthermore, psoriasis vulgaris (PsV) patients receiving systemic therapy developed increases in adiponectin that correlated with reductions in Psoriasis Area and Severity Index (PASI), CRP, VEG-F, and resistin, which is associated with insulin resistance (Boehncke et al., 2011). In addition, imiquimod-induced psoriatic skin inflammation can produce global changes in glucose sensitivity and a pre-diabetes phenotype (Evans et al., 2020). Finally, common genetic factors may play a role, as a recent study found PsV patients carrying the obesity-related *FTO* risk allele to have higher mean PASI scores, insulin concentrations, BMI, and hip and waist circumferences (Tupikowska-Marzec et al., 2019).

It is important to recognize and treat the metabolic comorbidities of psoriasis as patients with diabetes and concurrent psoriasis have a higher risk of micro and macrovascular complications, which contribute to significant morbidity and mortality (Armstrong et al., 2015). Hypoglycemic medications of different categories have also been found to improve psoriasis progression via different mechanisms (Ip and Kirchhof, 2017). In a recent study, liraglutide reduced psoriasiform inflammation in obese diabetic mice, with improvements in PASI, insulin resistance, and glucose metabolism positively correlating with IL-23, IL-17, IL-22 and TNF-α levels (Chen et al., 2020).

Cardiovascular comorbidities in psoriasis and psoriatic arthritis

In addition to metabolic dysfunction, patients with PsV and PsA have a higher prevalence of cardiovascular (CV) risk factors such as dyslipidemia (Dreiher et al., 2008, Holzer et al., 2012, Ma et al., 2014, Mallbris et al., 2006), lipoprotein dysfunction (Ahlehoff et al., 2011, Cerman et al., 2008, Hjuler et al., 2017, Mehta et al., 2013, Mehta et al., 2012, Rivers et al., 2018, Sorokin et al., 2018), and adiposity (Sajja et al., 2018, Snekvik et al., 2017), and are at increased risk for cardiovascular events, including myocardial infarction (MI), stroke, and cardiovascular death (Ahlehoff et al., 2011, Brauchli et al., 2009, Gelfand et al., 2010, Gelfand et al., 2011, Gelfand et al., 2006, Gelfand et al., 2007, Hu and Lan, 2017, Kimball et al., 2010, Kurd and Gelfand, 2009, Mehta et al., 2010, Mehta et al., 2013, Mehta et al., 2011a, Neimann et al., 2006, Noe et al., 2018, Ogdie et al., 2015). Furthermore, psoriasis is associated with a greater presence and extent of vascular inflammation as assessed by 18F-fluorodeoxyglucose positron emission tomography with computed tomography (CT) (Dey et al., 2017, Mehta et al., 2011b, Naik et al., 2015, Youn et al., 2015), lipid-rich non-calcified coronary disease, coronary artery calcium by CT (Elnabawi Y. A. et al., 2019, Joshi et al., 2018, Lerman et al., 2017, Mansouri et al., 2016, Staniak et al., 2014), and carotid as well as femoral atherosclerotic plaques by ultrasound (Di Minno et al., 2011, Eder et al., 2013, Eder et al., 2017).

The association between psoriasis and cardiovascular disease is thought to be mediated by the following: chronic low-grade inflammation, which is known to promote atherosclerosis (Sajja et al., 2018); adipokines, which induce inflammation and the development of CV factors (Hu and Lan, 2017); and endothelial injury induced by low-density granulocytes (Teague et al., 2019).

Although cardiovascular comorbidities are the major contributor to decreased life expectancy in patients with psoriasis, CV risk factors are often undertreated in psoriasis (Armstrong et al., 2013, Kimball et al., 2012). In a large cohort study, the Mediterranean diet was inversely associated with the severity of psoriasis after adjustment for BMI (Phan et al., 2018). It is therefore critically important to include education and preventive measures, such as promotion of a healthy lifestyle, weight reduction, and control of blood pressure, cholesterol levels, and insulin resistance in the treatment of psoriasis and PsA (Elmets et al., 2019a, Greb et al., 2016, Grundy et al., 2018, Harrington et al., 2017, Lloyd-Jones et al., 2018, Sajja et al., 2018). Recently, new guidelines were released emphasizing the importance of using systemic therapy to control the chronic low grade inflammation that is thought to be responsible for the development of CVD and other comorbidities (Elmets et al., 2019a).

Psychosocial comorbidities of psoriasis and itch

There is emerging evidence of a skin-brain axis in patients with psoriasis. A recent meta-analysis demonstrated an association between the onset and exacerbation of psoriasis with a preceding stressful event (Snast et al., 2018). Psoriasis patients have an increased prevalence of anxiety (Fleming et al., 2017) and depression (Cohen et al., 2016). Mechanistically, stress and shame due to the stigmatization of visible lesions may provoke depressive symptoms and, conversely, psychiatric comorbidity may worsen psoriasis severity via shared

inflammatory pathways (Torales et al., 2020). This bidirectionality is demonstrated by improved PASI correlating with a reduction in anxiety and depression symptoms (Gordon et al., 2018) and the use of serotonin reuptake inhibitors (SSRIs) decreasing the need to escalate therapy (Thorslund et al., 2013).

Itch may also be an important cause of anxiety and depression in patients with psoriasis. Pruritus intensity is positively correlated with more severe anxiety and depression in psoriasis patients (Mrowietz et al., 2015). Psoriatic itch also has a profound, negative impact on quality of life, and is associated with sleep disturbance including insomnia (Hawro et al., 2020, Kaaz et al., 2019), all of which are linked to psychiatric comorbidities in psoriasis (Gupta et al., 2016). Anxiety may in turn exacerbate pruritus (Sanders and Akiyama, 2018). The interconnection between psoriasis, pruritus, anxiety, and depression likely has a biologic basis. Murine models of contagious itch (Yu et al., 2017) and chronic itch (Jeong and Kang, 2015) demonstrate significant activation of brain regions involved in generating anxiety, such as the hippocampus and amygdala (Shekhar et al., 2005). Psoriatic itch may actually induce microstructural changes in the brain. A recent study showed that psoriasis patients who were exposed to videos of other individuals scratching exhibited changes in the white matter and functional connectivity of their brains (Najafi et al., 2020). Furthermore, regions of the brain that were shown to have higher connectivity in these patients included the bilateral cingulate gyri as well as the insula, regions known to be involved in the stress response (Golpanian et al., 2020).

At the molecular level, the inflammatory cytokine, IL-17A, is a key mediator of itch, anxiety, and depression. Elevated mRNA transcripts for IL-17A are associated with itch in psoriatic patients (Nattkemper et al., 2018). In murine models of psoriasis, overexpression of IL-17A correlated with increased NFκB and p38MAPK signaling, intracranial inflammatory mediators, and depression-like symptoms. Administration of anti-IL-17A therapy decreased NFκB and p38MAPK signaling and reversed depression-like symptoms (Nadeem et al., 2017). The anti-IL-17A agent, ixekizumab, demonstrated significant improvements in itch severity in multiple phase 3 clinical trials as early as week 1 of treatment and through 60 weeks, and remarkably, improvement in itch preceded clearing of the rash in 65% of patients (Kimball et al., 2018, Yosipovitch et al., 2018b). Ixekizumab was also recently shown to result in clinically meaningful improvements in genital itch and sexual activity as early as week 2 (Ryan et al., 2018, Yosipovitch et al., 2018a). Secukinumab also demonstrated rapid improvements in patient-reported itching and pain within the first 4 weeks of treatment (Yosipovitch et al., 2019).

Neurotransmitters and neuropeptides, which are both produced by and act upon the skin, are also thought to be important mediators of the skin-brain axis (Hunter et al., 2015). A recent study analyzing gene expression in skin from itchy patients with psoriasis found that the neuropeptide, substance P, and its receptor, neurokinin (NK)-1R, two molecules classically known to be involved in itch transmission, were overexpressed in pruritic psoriatic skin and pruritic atopic dermatitis skin (Nattkemper et al., 2018). Recently, serlopitant, an oral NK-1 receptor antagonist, was found to significantly reduce psoriatic pruritus (Pariser et al., 2020), although it is not yet FDA-approved for this indication.

Finally, psychosocial interventions such as family constellation seminars (FCS) examining transgenerational family dynamic patterns have been shown to reduce itch in psoriatic patients (Jafferany et al., 2019).

Targeted systemic therapies for psoriasis and psoriatic arthritis

As the understanding of the pathogenesis of psoriasis and its comorbidities continues to grow, treatment for psoriasis and PsA has improved and expanded. While this section will focus primarily on newer systemic targeted therapies, recent guidelines have been issued for the use of topical medications, traditional oral systemic therapies, and phototherapy (Elmets et al., 2019b, Menter et al., 2020).

Targeted oral systemics—Apremilast is an inhibitor of PDE-4 and FDA-approved for the treatment of psoriasis and PsA, with a PASI75 response rate for psoriasis of 29–33% at week 16 (Papp et al., 2015, Paul et al., 2015) and an ACR20 response rate between 32–40% at week 16 (Cutolo et al., 2016, Kavanaugh et al., 2014). Apremilast has a favorable safety profile and does not require routine laboratory monitoring. Apremilast is not associated with reactivation of tuberculosis and has been safely used in psoriasis patients with concurrent HIV, hepatitis B, and hepatitis C (Kaushik and Lebwohl, 2019, Keating, 2017). Apremilast may be especially useful in obese patients and in those with difficult to treat subtypes such as palmoplantar pustulosis (Bissonnette et al., 2016, Papp et al., 2015, Paul et al., 2015).

Tofacitinib, an inhibitor of Janus kinases (JAK), is FDA-approved for the treatment of PsA, and has demonstrated ACR 20 response rates between 47–61% in patients who were previously recalcitrant to conventional disease modifying therapies (DMARDs) or TNF-α inhibitors (Gladman et al., 2017, Mease et al., 2017). Adverse effects associated with tofacitinib include an increased risk of infections, including reactivation of latent tuberculosis and serious infections such as pneumonia, herpes zoster, and appendicitis, melanoma, and non-melanoma skin cancer (Strober et al., 2019). Tofacitinib has also been associated with elevated cholesterol, dose dependent decreases in hemoglobin and neutrophil count, and dose-dependent increases in hepatic transaminases (Strober et al., 2019).

Several novel oral agents are currently being studied for use in psoriasis and PsA. Among them is the small molecule deucravacitinib (formerly known as BMS-986165), which blocks Tyk2, a Janus kinase involved in signal transduction for IFN-α, IL-12, IL-23, and other cytokines known to be important in psoriasis pathogenesis (Papp et al, 2018). Lastly, brepocitinib (PF-06700841), a Jak1/Tyk2 inhibitor, has produced significant reductions in PASI in Phase 2 clinical trials (Forman et al., 2020).

Biologic therapies—Biologic therapies have revolutionized the treatment of psoriasis and PsA. Currently, there are twelve FDA-approved biologics for psoriasis and PsA that can be grouped into three major families: TNF-α inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol, golimumab) and the newer biologics that inhibit IL-17 (secukinumab, ixekizumab, brodalumab) or IL-23 (ustekinumab [which also inhibits IL-12], guselkumab, tildrakizumab, risankizumab). The biologics differ in their efficacy for cutaneous disease, joint disease, and cardiometabolic comorbidities as well as their safety profiles (Table 1) (Armstrong et al., 2020). While the choice of biologic therapy should be made based on

the individual patient, general guidelines are available to guide clinical care (Menter et al., 2019).

In network analyses and head-to-head comparisons, newer anti-IL-17 and anti-IL-23 agents such as brodalumab, ixekizumab, and risankizumab generally demonstrate higher response rates than anti-TNF-α therapies and ustekinumab across multiple endpoints (e.g., PASI75, PASI90, PASI100) and over short-term and long-term follow-up periods (e.g., Week 12/16, Week 48/52, and multiple-year) (Table 1) (Armstrong et al., 2020, Kamata and Tada, 2020, Lebwohl et al., 2015, Mease et al., 2020, Reich et al., 2019, Sawyer et al., 2019). Furthermore, the newer biologics induce higher rates of complete skin clearance. At the molecular level, tissue from patients treated with IL-17 inhibitors or IL-23 inhibitors demonstrate more complete normalization of gene expression, cellular infiltration, and epidermal structural changes compared to those treated with anti-TNF-α therapy, highlighting the importance of IL-23-dependent Th17 and Tc17 cells in the immunopathogenesis of psoriasis (Hawkes et al, 2018).

Unlike their efficacy in skin disease, IL-17 inhibitors and TNF-α inhibitors have comparable efficacy for the treatment of psoriatic joint disease (Furue et al., 2018, Kamata and Tada, 2020, Ruyssen-Witrand et al., 2020). One head-to-head trial suggests that ixekizumab produced superior ACR50 response rates compared to adalimumab, while in another head-to-head trial, adalimumab showed superior ACR response rates compared to secukinumab (Strand et al., 2017). As some studies have suggested that axial inflammation is driven by IL-23 independent IL-17 producing cells and IL-23 inhibitors have not been effective for ankylosing spondylitis (Venken et al., 2019), IL-17 inhibitors and TNF-α inhibitors may be more effective for the management of PsA with axial involvement (Kamata and Tada, 2020), although the differences between axial PsA and ankylosing spondylitis are still being studied. By contrast, IL23 inhibitors have been shown to be superior to TNF-α inhibitors for enthesitis (Araujo et al., 2019).

In terms of therapeutic safety, TNF-α inhibitors have been associated with serious infection, reactivation of tuberculosis, reactivation of hepatitis B infection, demyelinating disorders, malignancy, congestive heart failure, and paradoxical psoriasis. While meta-analyses do not show an increased risk of serious infection in IL-17 inhibitors (Li et al., 2020, Yin et al., 2020, Yiu et al., 2016), they are associated with a higher incidence of mucocutaneous candidiasis (Blauvelt, 2016). IL-17 inhibitors are also uniquely associated with both new onset and exacerbation of pre-existing inflammatory bowel disease, and in the case of brodalumab, suicide (Lebwohl et al., 2018). These adverse effects have *not* been observed with IL-23 inhibitors and a recent meta-analysis suggests that anti-IL-23 therapy has a lower overall risk of adverse events (AEs) compared to IL-17 inhibitors, although the risk of serious AEs was similar (Cui et al., 2018) (Table 1). These safety profiles follow what is known about the broad role of TNF-α in systemic inflammation and systemic infections compared to the narrower role of IL-23 and IL-17 in mucocutaneous defense (Blauvelt et al, 2015b). Overall, combining safety and efficacy data, biologics are more efficacious and safer than non-targeted systemics (e.g. methotrexate and cyclosporine) for psoriasis, which act more broadly on the immune system.

Impact of biologics on psoriatic comorbidities—While it is widely thought that biologics impact systemic inflammation and likely provide benefit in relation to comorbid conditions, the strongest evaluation has been in cardiometabolic health. TNF-α inhibitors, which have had the longest post-marketing follow-up, are associated with a reduction in MI in retrospective cohort studies (Wu et al., 2017, Wu and Poon, 2014, Wu et al., 2013, Wu et al., 2012). TNF-α inhibitors have also been associated with stabilization of coronary artery plaque (Elnabawi Y. A. et al., 2019), reduction in coronary artery inflammation (Elnabawi Youssef A. et al., 2019), and reduction in vascular inflammation by positron emission tomography (Dey et al., 2017). However, recent randomized controlled trials (RCTs) did not demonstrate beneficial effects on vascular inflammation when compared to placebo (Bissonnette et al., 2017, Mehta et al., 2018).

Small studies have found that the use of anti-IL-12/23 therapy was associated with improved myocardial function (Ahlehoff et al., 2016, Ikonomidis et al., 2017), decreased vascular inflammation (Kim et al., 2019), and significant improvements in leptin concentration and leptin receptor expression on macrophages (Voloshyna et al., 2016). However, a double-blinded RCT showed that IL-12/23 inhibition reduced vascular inflammation at 12 weeks, but not at 52 weeks, suggesting that the beneficial effects may be transient (Gelfand et al., 2020b, Gelfand et al., 2018).

Secukinumab, an IL-17 inhibitor, was found to have a neutral impact on flow-mediated dilation by ultrasound (von Stebut et al., 2019) and vascular inflammation in the aorta when compared to placebo (Gelfand et al., 2020c). A recent study using coronary computed tomography angiography showed that biologic therapies, including IL-17 inhibitors, were associated with stabilization of high-risk coronary plaque necrotic core when compared to nonbiologic therapy over one-year of treatment (Elnabawi Y. A. et al., 2019) (Figure 1).

While these studies demonstrate encouraging improvements in radiographic changes and serologic markers, there are currently no RCTs that examine the impact of psoriasis or PsA targeted therapies on the development of cardiovascular events. A large meta-analysis including 38 randomized controlled trials showed no significant difference in risk of major adverse cardiac events in psoriasis treated with biologic therapies (IL-12/23 inhibitors, TNF-α inhibitors, and IL-17A inhibitors; however, these studies were designed to test the efficacy of biologics on psoriasis clearance rather than cardiovascular events (Rungapiromnan et al., 2017).

Interestingly, data from RCTs investigating the role of other anti-inflammatory medications in the secondary prevention of cardiovascular events suggests that targeted biologic therapies for psoriasis and PsA may hold similar promise. For example, the randomized, placebo-controlled COLCOT trial showed that patients with a prior MI who received daily colchicine had a significantly lower incidence of stroke and angina leading to coronary revascularization (Tardif et al., 2019). Similarly, the CANTOS RCT found that patients with a history of MI who received canakinumab, a monoclonal antibody targeting interleukin-1β, had a significantly lower rate of unstable angina leading to coronary revascularization and a trend towards decreased risk of MI even in the absence of significant reductions in cholesterol levels (Ridker et al., 2017).

New biologic therapies for psoriasis and PsA—New advances in biologic therapies continue to raise the bar for treatment of psoriasis and PsA. There are two new injectable biologics in late-stage phase 3 studies that are likely to reach the market in the next several years. The first is bimekizumab, a novel anti-IL-17A/IL-17F monoclonal antibody (Blauvelt et al, 2020), and the second is mirikizumab, another selective anti-IL-23 monoclonal antibody (Reich et al, 2019). Of note, high levels of efficacy reported with bimekizumab highlight the role of IL-17F in psoriasis pathogenesis (over and above IL-17A alone), which is a cytokine that shares 50% homology with IL-17A, is found in abundance in psoriatic tissue, and shares many pro-inflammatory features with IL-17A (Blauvelt et al, 2020).

Despite the exciting new advances in biologic treatments for psoriasis and PsA, issues of access and affordability remain to be addressed.

Management of psoriatic disease in the age of COVID-19—The recent COVID-19 pandemic presents a new challenge for the management of psoriatic disease. For the many psoriatic disease patients who depend on long-term systemic therapy, there is concern that suppressing the immune system may leave them more vulnerable to SARS-CoV-2 infection, the virus that causes COVID-19. On the other hand, JAK/Stat inhibitors, anti-IL-17 agents, and TNF-α inhibitors have been proposed as potential therapies for the cytokine storm that is thought to be responsible for worse outcomes in Covid-19 (Feldmann et al., 2020, Pacha et al., 2020, Richardson et al., 2020). In the absence of definitive studies, data can be extrapolated from the adverse events reported in clinical trials (Brownstone et al., 2020, Lebwohl et al., 2020). Multiple case series from Europe and the United States, suggest that long-term use of biologics is not associated with worse COVID-19 outcomes of patients with autoimmune disease (Fredi et al., Gelfand et al., 2020a, Haberman et al., 2020, Jovani et al., 2020, Norsa et al., 2020). In light of the available evidence, recent guidelines recommend that in most cases, patients who are not infected with SARS-CoV-2 may continue their biologic or oral therapies and receive mRNA based COVID-19 vaccination without interruption in therapy (Gelfand et al., 2021).

Conclusion

New advances in research have enhanced our understanding of the effects of systemic psoriatic inflammation in the presentation of comorbid conditions. As our understanding of the systemic manifestations of psoriasis evolves, so too has our approach to management. The future of psoriatic disease treatment lies in a holistic approach that addresses health issues beyond the skin. While targeted therapies will provide part of the solution, early recognition and management of comorbidities as well as lifestyle modifications will be important components of an integrated treatment plan.

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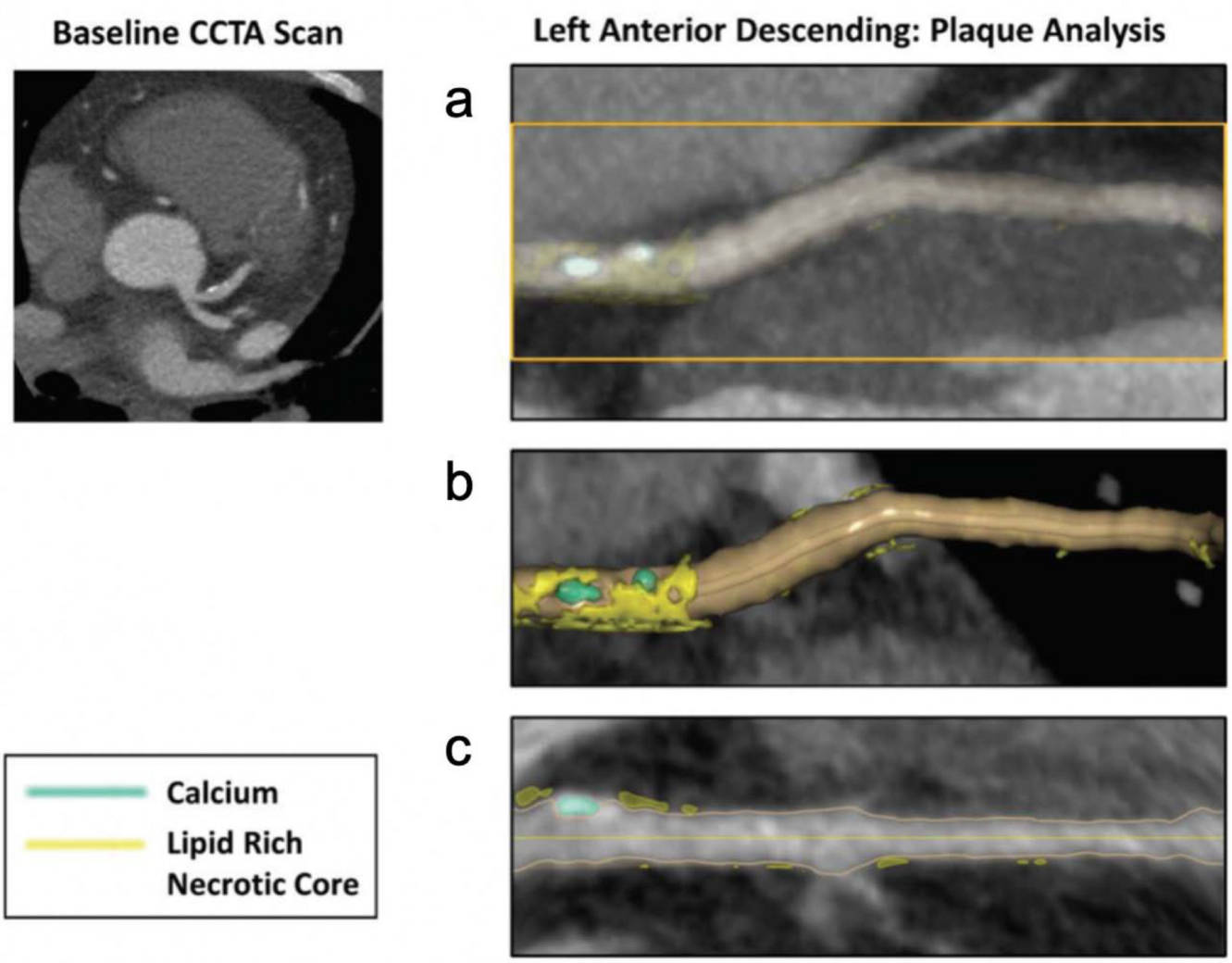

Figure 1. Proximal Left anterior descending artery, with plaque identified at baseline.

(a) Coronary artery visualized from coronary CT angiography (CCTA) scan with overlying segmentation of artery and derivation of plaque characteristics (transparent). (b) Three-Dimensional segmentation of artery in gold with derived plaque characteristics displayed; lipid-rich necrotic core (LRNC) in yellow and calcified (CALC) plaque in green. (c) Longitudinal planar view through midline of coronary artery with color overlap displaying plaque characteristics.

*Image courtesy of NHLBI (Mehta Lab, under submission in Journal of *CIRC CV* Imaging).

Table 1.

Biologics for Psoriatic Disease: Dose, Efficacy, Indication and Features

Drug Name	Family	Approval Year	PsO Efficacy During Placebo-Controlled Period (*PASI 90)	Additional Important Features
etanercept (Enbrel®)	TNF-α blocker	2004	Week 12: **40%** (Papp et al., 2005) and **21%** (Tyring et al., 2006)	Soluble receptor; MD:& every week; black box warnings: serious infections, malignancies; approved for PsA^
infliximab (Remicade®)	TNF-α blocker	2006	Week 10: **57%** (Reich et al., 2005)	IV# administration; dosed by weight; MD: every 8 weeks; black box warnings: serious infections, malignancies; approved for PsA
adalimumab (Humira®)	TNF-α blocker	2008	Week 16: **45%** (Menter et al., 2008) and **51.3%** (Saurat et al., 2008)	MD: every 2 weeks; black box warnings: serious infections, malignancies; approved for PsA
certolizumab (Cimzia®)	TNF-α blocker	2018	Week 16: **43.6%**, **55.4%** (Gottlieb et al., 2018), and **49.1%** (Lebwohl et al., 2018)	Fab portion only/does not cross placenta; MD: every 2 weeks; black box warnings: serious infections, malignancies; approved for PsA
secukinumab (Cosentyx®)	IL-17A blocker	2015	Week 12: **59.2%**, **54.2%** (Langley et al., 2014), and **60.3%** (Blauvelt et al., 2015a)	MD: every 4 weeks; approved for PsA
ixekizumab (Taltz®)	IL-17A blocker	2016	Week 12: **70.9%** (Gordon et al., 2016), **70.7%**, and **68.1%** (Griffiths et al., 2015)	MD: every 4 weeks; approved for PsA
brodalumab (Siliq® marketed as Kyntheum® in Europe and Lumicef® in Japan)	IL-17RA blocker	2018	Week 12: **70.3%** (Papp et al., 2016), **70%**, and **69%** (Lebwohl et al., 2015)	Blocks activity of IL-17A, IL-17C, IL-17E, and IL-17F; MD: every 2 weeks; black box warning: suicidal ideation and behavior
ustekinumab (Stelara®)	IL-12/IL-23 blocker	2009	Week 12: **41.6%/ 36.7%** (45/90 mg) (Leonardi et al., 2008) and **42.3%/50.9%** (45/90 mg) (Papp et al., 2008)	Two different doses based on weight; MD: every 12 weeks; approved for PsA
guselkumab (Tremfya®)	IL-23 blocker	2017	Week 16: **73.3%** (Blauvelt et al., 2017) and **70.0%** (Reich et al., 2017)	MD: every 8 weeks; approved for PsA
tildrakizumab (Ilumya®)	IL-23 blocker	2018	Week 12: **35%** and **39%** (Reich et al., 2017)	MD: every 12 weeks
risankizumab (Skyrizi®)	IL-23 blocker	2019	Week 16: **75.3%**, **74.8%** (Gordon et al., 2018), and **73.2%** (Blauvelt et al., 2020a)	MD: every 12 weeks

*PASI 90, percentage of patients who achieve at least 90% improvement from baseline in the Psoriasis Area Severity Index (an indication of highly successful therapy)

&MD, maintenance dose

^PsA, psoriatic arthritis

#IV, intravenous