Choosing the Appropriate Target for the Treatment of Psoriatic Arthritis: TNFα, IL-17, IL-23 or JAK Inhibitors?

Chrysoula G. Gialouri, Gerasimos Evangelatos, George E. Fragoulis

*These authors contributed equally.

1First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, “Laiko” General Hospital, Athens, Greece

ABSTRACT

Psoriatic arthritis (PsA) is a highly heterogeneous disease. Apart from arthritis and psoriasis, other manifestations can also occur, including enthesitis, dactylitis, axial-, nail-, eye- and bowel- involvement. Comorbidities are also frequent in the setting of PsA, with cardiovascular disease and mental-health disorders being the most frequent. The Rheumatologist’s arsenal has many different treatment options for treating PsA. Despite their effectiveness, there are some differences in terms of efficacy and safety that might affect clinician’s decision for one or the other drug. Comparing biologic DMARDs and JAK-inhibitors, one could say that they have similar effectiveness in terms of musculoskeletal manifestations. However, anti-IL-17 and anti-IL-23 drugs seem to be more effective for skin manifestations. In contrast, JAK-inhibitors and etanercept might be less effective for these manifestations. Inflammatory bowel disease and uveitis are non-responsive to etanercept and anti-IL-17 drugs. As regards to comorbidities, data are scarce, but future studies will shed light on possible differential effect of bDMARDs or JAK-inhibitors. Safety is always an important drive for choosing the appropriate treatment. Infections are the most common adverse event of these drugs. Etanercept and anti-IL-17 drugs are safer for patients having latent tuberculosis, while herpes zoster is more common in individuals receiving JAK-inhibitors. Finally, venous thromboembolism risk, should be taken into account when JAK-inhibitors are used. In this review, we comparatively present, as outlined above, the various aspects that could affect the choice of the appropriate bDMARD or JAK-inhibitor for the treatment of a PsA patient.

Keywords: psoriatic arthritis, biologic DMARDs, JAK-inhibitors, treatment, comorbidities
that about 30% of PsA patients meet the diagnosis for metabolic syndrome (MetS).\textsuperscript{4} Also, depression is a co-morbidity frequently observed with a prevalence ranging between 15% and 20%\textsuperscript{2}.

Pathophysiology of PsA is based on a complex interplay between environmental stimuli (infections, trauma, smoking, stress etc.), gut microbiome and mechanical stress, in genetically predisposed individuals.\textsuperscript{5} Upon this background, myeloid dendritic cells activated by interferon (IFN)-\alpha and other pro-inflammatory mediators produced by innate immune cells (plasmacytoid dendritic cells and natural killer T cells, macrophages, keratinocytes), drive through IL-12 and IL-23 to Th1 and Th17 responses, respectively. The former lead to production of TNF-\alpha, IFN-\gamma and the latter of IL-17, IL-22.\textsuperscript{6} Subsequently, these cytokines mediate their effect in a variety of cells, like resident skin cells, synovial tissue cells, osteoblasts and osteoclasts, leading to disease initiation and/or perpetuations.\textsuperscript{5}

There are several therapeutic options in PsA, including NSAIDs, glucocorticoids, conventional disease modifying antirheumatic drugs (cDMARDs; methotrexate, sulfasalazine, leflunomide, cyclosporin), targeted synthetic (ts) DMARDs [JAK-inhibitors (JAKi) and apremilast] and biologic DMARDs (bDMARDs), including regimes against TNF, Interleukin (IL)-17 and IL-23. Treatment, especially with bDMARDs, in patients with PsA has come with some concerns for safety, including risk for malignancies, infections and cardiovascular events. Choice of the drug is based on several features, like efficacy in the various facets of PsA, comorbidities, contraindications (eg, NSAIDs and gastric ulcers), safety profile (eg, some biologics are safer for TB than the others) and other aspects like route of administration. Aim of our review is to describe how the clinician chooses the appropriate treatment, among bDMARDs and JAKi (also known as JAKinibs), based on the above-mentioned axes.

### COMPARISON OF EFFICACY

Evidence from clinical trials and observational studies have revealed differences regarding the efficacy of bDMARDs and JAKi in various aspects of PsA (Figure 1).

#### Peripheral Arthritis

European Alliance of Associations for Rheumatology (EULAR), American College of Rheumatology (ACR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines suggest that treatment with a cDMARD should be initiated in most PsA patients with active peripheral arthritis.\textsuperscript{7-9} For those who have inadequate response or cannot tolerate cDMARDs, a bDMARD should be commenced. Regarding articular outcomes, all TNF-inhibitors (TNFi), IL-17 inhibitors, ustekinumab (an IL-12/23 inhibitor), guselkumab (an IL-23 inhibitor) and tofacitinib (a JAK1-3 inhibitor) have been proven effective in clinical trials. In a recent meta-analysis, TNFi, IL-17 inhibitors and ustekinumab had all increased ACR20, ACR50 and ACR70 responses versus placebo, with comparable risk ratios.\textsuperscript{10} Secukinumab exhibited similar efficacy with adalimumab in arthritis outcomes in EXCEED study, a head-to-head double-blind randomised control trial.\textsuperscript{11} As for ixekizumab, another IL-17 inhibitor, it showed numerically similar results to adalimumab in bDMARD-naïve patients with active PsA in SPIRIT-P1 study.\textsuperscript{12} To be mentioned, the latter study was not powered to directly compare the two drugs.\textsuperscript{10,12} Ustekinumab initially demonstrated numerically lower efficacy than other bDMARDs, by indirect comparison, as measured by ACR20, ACR50 and ACR70 in pivotal

| Arthritis | Anti-TNF | Etanercept | Anti-IL-17 | Anti-IL-23 | JAKi |
|-----------|----------|------------|------------|------------|------|
| Axial     |          |            |            |            |      |
| Skin      |          |            |            |            |      |
| Enthesitis|          |            |            |            |      |
| Dactylitis|          |            |            |            |      |
| Nail disease |        |            |            |            |      |
| *Eye      |          |            |            |            |      |
| **Bowel** |          |            |            |            |      |

*Marketed for uveitis: only adalimumab; **Marketed for Crohn's disease: adalimumab, infliximab, certolizumab, ustekinumab. Marketed for ulcerative colitis: adalimumab, infliximab, golimumab, ustekinumab, tofacitinib. VTE: venous thromboembolism; PE: pulmonary emboli; JAKi: JAK inhibitors.
studies PSUMMIT-1 and PSUMMIT-2. However, in ECLIPSA, a small randomized open-label study, ustekinumab was compared to TNFi (specifically adalimumab, certolizumab, etanercept and infliximab) and showed similar effect on arthritis (p=0.95). Collectively, TNFi and inhibitors of IL-17 and IL-12/23 (secukinumab, ixekizumab, ustekinumab) had similar ACR20 responses (risk ratio for TNFi 2.23, 95% CI 1.60–3.11 and pooled risk ratio for non-TNFi 2.30, 95% CI 1.94–2.72). As for tofacitinib, its articul effectiveness is comparable to most bDMARDs. However, a recent network meta-analysis showed that in TNF-IR patients, etanercept, golimumab and infliximab seem to achieve better ACR20 responses compared to tofacitinib, while in TNF-inadequate responders (TNF-IR) PsA patients, certolizumab has been found to perform better than tofacitinib in peripheral arthritis management. Gusekumab was recently approved by FDA for the treatment of active PsA. In pivotal studies DISCOVER-1 and DISCOVER-2, gusekumab exhibited ACR20 response in 52-64% of patients with active PsA at 24 weeks, but no direct comparison with other drugs is available till now. Other IL-23 inhibitors, such as risankizumab and tildrakizumab, are currently under investigation for the treatment of active PsA. Finally, all TNFi, IL-17 inhibitors, ustekinumab and tofacitinib are associated with improvement of physical functioning in PsA patients, as assessed by health assessment questionnaire-disability index (HAQ-DI). TNFi did not differ significantly from newer agents (inhibitors of IL-17 and IL-12/23) in this parameter (pooled risk ratio of 0.29 [95% CI –0.39 to –0.19] versus –0.26 [95% CI –0.31 to –0.22]). To be mentioned, in TNF-IR patients, secukinumab 150mg/4weeks did not lead to significant change of HAQ-DI from baseline. Finally, numerically comparable reduction in HAQ-DI values was reported with ixekizumab and adalimumab in SPIRIT-P1 study.

Axial disease

Scarce data are available for bDMARD effectiveness in psoriatic spondylitis. MAXIMISE is the only clinical trial with focus on axial disease in patients with PsA. In this study, both secukinumab doses 150mg and 300mg/4 weeks, after loading dose, achieved statistically significant ASAS20 response compared to placebo (19). In patients with PsA, treatment with etanercept led to improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Disease Functional Index (BASFI) scores. Based on data from Axial SpA (AxSpA), EULAR and ACR suggest that PsA patients with axial disease should start a TNFi after NSAIDs failure; an IL-17 inhibitor is the suggested alternative if there are contraindications for TNFi or severe skin involvement. Noteworthy, blockade of IL-23 is not effective in AxSpA, as indicated from negative results from ustekinumab and guselkumab trials. However, it still remains to be defined whether results regarding therapeutic efficacy are transferable from AxSpA to axial-PsA. Finally, several JAKinibs are currently under investigation for the treatment of AxSpA, with promising initial results. Tofacitinib achieved significantly higher (Assessment of SpondyloArthritis-20) ASAS20 and ASAS40 rates compared to placebo in a phase II trial in bDMARD-naive patients with active ankylosing spondylitis.

Psoriasis

All TNFi, IL-17 inhibitors, IL-12/IL-23 and IL-23 inhibitors are approved for plaque psoriasis. As shown in a recent meta-analysis, Psoriasis Area Severity Index (PASI) 75 and PASI90 responses were comparable between TNFi (considered as a class), IL-17 inhibitors and ustekinumab in patients with PsA. Another meta-analysis showed that IL-17 inhibitors, IL-23 inhibitors and infliximab are associated with increased rates of PASI90, compared to ustekinumab and other TNFi. Importantly, etanercept has shown lower rates of PASI75 response than the rest TNFi, while adalimumab proved better than certolizumab in achieving PASI90 response. Moreover, etanercept was proven inferior to ustekinumab, secukinumab and ixekizumab in psoriasis. Ustekinumab performed better than TNFi in psoriatic skin disease (p=0.03) in ECLIPSA study. Newer IL-23 inhibitors, especially guselkumab and risankizumab, have achieved impressive PASI75 and PASI90 scores, even better than ustekinumab, in clinical trials. As expected, guselkumab was superior to adalimumab in a head-to-head comparison in psoriasis patients. Taking the above data into account, IL-17 and IL-12/23 inhibitors are preferred over TNFi in PsA patients with severe skin disease, according to EULAR guidelines.

Tofacitinib, on the other hand, seems inferior to bDMARDs in skin manifestations of PsA, especially in the dose of 5mg BID. Based on a recently published meta-analysis, golimumab, infliximab and ixekizumab were associated with increased PASI75 response compared to tofacitinib in TNFi-naive patients. In TNF-IR patients, tofacitinib 5mg BID did not differ significantly from placebo in PASI75 rates.

Enthesitis

Enthesitis has been characterised as a hallmark of PsA, occurring in about 35-50% of patients. Enthesitis in clinical trials is usually quantified with Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index or Leeds Enthesitis Index (LEI). NSAIDs are widely used in active enthesitis in clinical practice, but are less effective in chronic enthesitis. As cDMARD have been proven ineffective in the treatment of enthesitis, EULAR, ACR and GRAPPA guidelines suggest the initiation of a bDMARD in patients with active enthesitis (7-9).
All TNFi, IL-17 inhibitors secukinumab and ixekizumab, ustekinumab and tofacitinib have exhibited satisfactory results in PsA enthesitis.10,15,30,31 ECLIPSA study was the only study with enthesitis resolution as the primary outcome.14 In this open-label randomised controlled study, in about 74% of ustekinumab-treated patients and 41.7% of patients treated with a TNFi complete clearance of enthesitis was noted at 24 weeks (p=0.018).14 In contrary, a recent meta-analysis showed comparable mean risk ratios for enthesitis resolution between IL-17 inhibitors, TNFi and ustekinumab, compared to placebo (2.31, 1.99 and 1.41, respectively).10 Moreover, in another meta-analysis, TNFi demonstrated similar rates of enthesitis resolution at week 24, compared to IL-17 and IL-12/23 inhibitors.15 In EXCEED, a head-to-head clinical trial of secukinumab versus adalimumab in PsA, both drugs had similar rates of enthesitis remission, as defined by LEI (61% vs 54%, p=0.150).11 Moreover, ixekizumab showed numerically greater enthesitis improvement versus adalimumab, especially in the dose of 80mg every 2 weeks, in the SPIRIT-P1 study.15 Tofacitinib in the dose of 5mg twice daily had numerically lower improvement in LEI compared to adalimumab at 3 months, but the results of the two drugs were comparable at month 12.31 Thus, tofacitinib in the approved dose of 5mg BID might have a more delayed effect on enthesitis than adalimumab. Finally, in clinical trials, guselkumab led in enthesitis resolution in 40-50% at 24 weeks, depending on the dose applied (17, 18). Similar or even better results were reported on 56 weeks in a phase II trial.32

**Dactylitis**

Dactylitis is a characteristic manifestation of PsA and occurs in about half patients during the course of the disease.33 Although no controlled studies have been conducted regarding the efficacy of NSAIDs and local corticosteroids in dactylitis,33 these agents are frequently used by clinicians. As digital inflammation most times accompanies a generally active articular disease, EULAR and GRAPPA suggest that initiation of a cDMARD, mainly methotrexate, should be considered.7,9 Monoclonal antibody TNFi (certolizumab, infliximab, golimumab and adalimumab), IL-17 inhibitors, ustekinumab and tofacitinib have been proven effective on dactylitis in clinical trials.16,33 GO-DACT was the only trial that a dactylitis score change was the primary outcome.34 This trial demonstrated that the combination of golimumab plus methotrexate exhibited greater improvement of dactylitis, compared to methotrexate monotherapy, in methotrexate- and bDMARD-naïve patients.34 Although in clinical trials of ustekinumab a favourable effect on dactylitis was shown,35 a recent meta-analysis showed that the reduction of dactylitis was not statistically significant.10 On the other hand, in the same meta-analysis, IL-17 inhibitors and TNFi were both proved effective in dactylitis resolution (2.65 and 2.07 risk ratio versus placebo, respectively).10 It seems that TNFi and IL-17/IL-12/23 inhibitors have comparable efficacy in dactylitis.15 In EXCEED study, secukinumab and adalimumab did not differ significantly in dactylitis resolution rates (75% vs 70%, p=0.356).11 In addition, in SPIRIT-P1 study, ixekizumab and adalimumab showed similar rates of dactylitis amelioration.12 Finally, tofacitinib and adalimumab have also comparable results in Dactylitis Severity Score change in cDMARD-IR patients.16,31 To be noted, guselkumab was also proved effective in dactylitis; in guselkumab-treated PsA patients with dactylitis at baseline, 59-65% had remission of digital inflammation at 24 weeks.17,18 These results improved further at 56 weeks.32

**Nail involvement**

About 50% of psoriasis patients and 80% of patients with PsA have nail lesions.39,40 Nail Psoriasis Severity Index (NAPSI) has been utilized in most studies to quantify the extent of nail psoriasis. All TNFi, IL-17 inhibitors, ustekinumab, guselkumab, and tofacitinib have shown effectiveness in nail disease. EXPRESS study showed significant reduction in NAPSI score at weeks 10 and 24 of treatment with infliximab in patients with psoriasis.37 Data from psoriasis trials suggest that etanercept is effective in nail psoriasis.38 Adalimumab, golimumab and certolizumab have been proven effective in treating nail involvement in patients with PsA.12,38-40 Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis in 24 weeks and the improvement continued until week 52 of treatment.41 Sustained and strong improvement of nail psoriasis has been recently reported with secukinumab treatment.42 Moreover, significant NAPSI score improvement was reported in ixekizumab-treated PsA patients, numerically comparable to adalimumab.12 Importantly, guselkumab was also proven very effective in nail psoriasis, without significant difference from adalimumab.42 Finally, improvement in nail psoriasis has been reported with 16 weeks tofacitinib treatment and the result was maintained for at least 52 weeks.44

**Inflammatory bowel disease**

About 3.3% of PsA cases might express clinically evident IBD development,15 while subclinical intestinal inflammation can be detected in up to 40% of PsA patients.46 Only few data have been published regarding effectiveness of available drugs in PsA patients with concurrent IBD (Figure 1). Thus, management of these patients is based on data from IBD trials. Monoclonal antibody TNFi and ustekinumab are approved for the treatment of Crohn’s disease and ulcerative colitis.43 In 70 patients with IBD and psoriasis or PsA, the majority of patients achieved clinical remission of intestinal, skin and articular manifestations with ustekinumab.47 Etanercept and inhibitors of IL-17 have been proven ineffective in the treatment of IBD.23,48
On this basis, ACR recommends that PsA patients with concomitant IBD are preferably treated with a monoclonal antibody TNFi or ustekinumab. Nevertheless, the risk of IBD flare or new-onset IBD in patients treated with secukinumab is low.\(^6^9\) Regarding tofacitinib, it has been approved for active ulcerative colitis, so this makes tofacitinib a useful alternative in patients with PsA and ulcerative colitis. In contrary, tofacitinib has not been effective in Crohn’s disease.\(^5^0\) Finally, ongoing phase III clinical trials will examine the efficacy of guselkumab in Crohn’s disease and ulcerative colitis.

**Eye involvement**

From ocular manifestations of PsA, anterior uveitis is the most common and can affect up to 25% of PsA patients.\(^5^1\) Data on management of specific PsA-associated uveitis are lacking, thus, treatment modalities used for SpA-associated uveitis are applied. Adalimumab has been approved for non-infectious uveitis (Figure 1) and, along with infliximab, are the most potent bDMARDs in the treatment of SpA-associated uveitis.\(^5^2\) Certolizumab and golimumab have shown promising results in reducing uveitis flares; in contrary, etanercept was ineffective in uveitis (compared to adalimumab and infliximab) and might be associated with a slightly increased incidence.\(^5^2\) In a pooled analysis of 118 patients with non-infectious uveitis, secukinumab failed to reduce recurrence of ocular inflammation, but contributed in immunosuppressants use reduction.\(^5^4\) Ustekinumab and tofacitinib showed promising results in case reports and are currently under study in ongoing clinical trials.\(^5^2\) Ixekizumab and guselkumab have not been studied yet in non-infectious uveitis.\(^5^3\) Based on the aforementioned data, EULAR recommendations suggest that PsA patients with uveitis are treated with a monoclonal antibody against TNF, as a first- and second-line treatment.\(^7^\) Moreover, as uveitis can respond to methotrexate, ACR recommends the use of combination of bDMARD with methotrexate instead of bDMARD monotherapy in patients with PsA-associated uveitis.\(^8^\)

**COMORBIDITIES IN PSA: EFFICACY OF bDMARD AND JAK-INHIBITORS**

Cardiometabolic comorbidities and associated factors: obesity, DM, NAFLD, dyslipidemia, cardiovascular diseases

As mentioned above metabolic comorbidities and associated risk factors (eg, obesity, impaired glucose tolerance, dyslipidemia) are commonly encountered in PsA and strongly linked with morbidity and mortality in this setting.\(^3^\)

**Obesity**

Obesity is identified as an independent risk factor for PsA development in patients with psoriasis, as well as in healthy individuals.\(^5^5\) Additionally, adipose tissue and its mediators (ie, adipokines) seem to contribute to the perpetuation of inflammation in these patients. There is some evidence that anti-TNF treatment might result in weight gain, however it is not clear whether it concerns an increase in fat or free-fat mass.\(^5^6\) On the other hand, obesity is poor predictor for treatment response\(^5^6\)\(^,\)\(^5^9\); Treatment with TNFi is found to be less effective for achieving and sustaining remission.\(^5^8\)\(^,\)\(^6^0\)

A recent study by Ogdie et al revealed that among other factors, obesity was negatively associated with disease remission in patients starting TNFi (OR = 0.51, 95% CI 0.32–0.81).\(^6^1\) Furthermore, cohort studies based on Danish and Icelandic biologics registries including over 1000 PsA patients pointed out that obesity was a risk factor for TNFi withdrawal owing to reduced response.\(^5^2\) Data for other biologics in obese PsA patients are limited. There are findings indicating that Th17 cells and IL-17 play some role in the obesity-related inflammatory processes.\(^6^3\) Pantano et al. prospectively analysed 100 PsA patients receiving secukinumab for 6 months and found that overweight/obese patients (BMI≥ 25) had better clinical response (estimated using Disease Activity in Psoriatic Arthritis [DAPSA] score) than those with BMI<25 (p=0.05).\(^6^4\) In contrast, results from a retrospective study in PsO patients show inferior efficacy of secukinumab in those with BMI ≥ 30.\(^6^5\)

**Diabetes Mellitus**

DM is more prevalent among PsA patients, especially in women with more active disease, compared with the general population. The pathogenic linkage between PsA and DM is multifactorial. Among other cytokines, TNF-α plays a critical role leading to insulin resistance (IR) and higher levels of active endogenous cortisol, affecting in turn, glucose metabolism. Also, TNF-α downregulates adipokines which normally increase insulin sensitivity and have anti-atherogenic properties.\(^6^6\) Also, type 2 DM has been correlated with increased circulating Th17 cells and IL-17 levels,\(^6^7\) while the pleomorphic actions of JAKI do not allow any definite conclusions about their impact in glucose homeostasis. Although there is some evidence that TNFi might have some beneficial effect, it appears that treatment with bDMARDs, does not significantly alter glucose homeostasis. A prospective study, including PsA patients without DM, demonstrated that treatment with TNFi (adalimumab, infliximab and etanercept) up to 6 months, did not change fasting glucose levels (FGL).\(^6^8\) On the other hand, commencing TNFi in patients with inflammatory arthritis has been shown to lead in reductions in HbA1c. This effect, however, had comparable magnitude with patients receiving methotrexate (MTX), implying that this reduction might not be TNFi-specific.\(^6^9\) As regards IL-17-blocking reagents, thus far, large-scale studies including PsA/PsO patients receiving monoclo-
nal antibodies against IL-17A (ixekizumab, secukinumab) have not found any effect on glucose metabolism.\textsuperscript{70-73} Finally, data derived from two phase 3 studies (OPAL Broaden and OPAL Beyond) in PsA patients receiving JAKi, indicate that, irrespective of baseline metabolic state, tofacitinib was effective for patients with active PsA.\textsuperscript{74}

Non-alcoholic fatty liver disease
NAFLD comprises a spectrum of liver disease ranging from hepatic steatosis, steatohepatitis and liver fibrosis (LF) to cirrhosis and potentially carcinoma.\textsuperscript{75} In a meta-analysis the risk of NAFLD compared to non-psoriatic controls was elevated in patients with psoriasis and more pronounced in PsA patients (OR: 2.25, 95% CI: 1.37-3.71).\textsuperscript{76} Besides, insulin resistance and MetS are predisposing factors for NAFLD occurrence.\textsuperscript{77} It is not clear whether liver disease in PsA is promoted by the treatment administered -especially with methotrexate- or is associated with disease itself.\textsuperscript{56} Seitz et al. showed that the combination of TNFi with methotrexate (MTX) has a protective effect against development of LF in PsA patients compared to MTX monotherapy,\textsuperscript{78} while in a retrospective study, using data derived from claims database, TNFi use was not associated with a protective effect for PsA patients.\textsuperscript{79} Hitherto, there are no data about the possible role of IL-17 inhibitors or other bDMARDs in NAFLD/hepatic steatosis, although there are some data supporting that Th-17 and IL-17 appear to be improved in both genders, regardless of traditional cardiovascular risk factors.\textsuperscript{80} The beneficial vascular effects of anti-cytokine immune therapy is correlated with improved clinical outcomes. Although data are more robust for other inflammatory arthritis, like RA, for PsA only a few studies have evaluated the effect of bDMARDs on CVD risk, let alone the potential differences among different bDMARDs and JAKinibs. A meta-analysis including only 6 studies for PsO/PsA, shown that TNFi therapy is associated with lower risk of all CVD, than the topical treatment.\textsuperscript{81} In line with these findings, another meta-analysis showed remarkable reduction of MI incidence and risk of CVD with TNFi, compared with topical therapy, phototherapy or methotrexate treatment (90). On the other hand, when other licensed bDMARs are compared with TNFi, no differences were found. In a large cohort study including 60028 patients with PsO or PsA from US, the risk for atrial fibrillation or major adverse CVD events did not diverge between groups treated with ustekinumab (IL-12/IL-23 inhibitor) or TNFi.\textsuperscript{82} As for JAK-inhibitors (JAKi), short-term safety data from OPAL Balance clinical trial, including > 650 PsA patients, do not indicate increased risk for major adverse cardiovascular events comparable to other treatment groups.\textsuperscript{83}

Dyslipidemia
Dyslipidemia is also a common feature in PsA. However, the abnormalities in the lipid profiles in these patients are ill-defined. Findings from a limited number of studies support that PsA patients, display lower levels of TC, HDL-C and LDL-C, but higher levels of TG compared to individuals without PsA.\textsuperscript{84} It is also unknown if the lipid paradox described in RA\textsuperscript{52} operates also in PsA. Studies about the effect of bDMARDs in lipid profile of PsA patients are lacking. In a cohort study including 118 PsA patients, 5-years treatment with etanercept led to a modest increase of TC, HDL-C and LDL-C, TC/HDL-C ratio remained unchanged, whereas ApoB/ApoA-I ratio decreased implying thus a cardioprotective effect.\textsuperscript{85}

Cardiovascular Disease
It is well recognized that cardiovascular risk is increased in patients with inflammatory arthritis.\textsuperscript{51,84} Many hypotheses have been formed to explain it; however, chronic inflammation appears to be the main culprit. In particular for PsA, available data from a meta-analysis indicate that it is associated with increased risk of cardiovascular disease (CVD) and 55% higher risk of developing an incident cardiovascular event (myocardial infarction [MI], cerebrovascular diseases and heart failure [HF]), compared with the general population.\textsuperscript{86} The higher cardiovascular risk cannot be fully explained by the traditional cardiovascular risk factors and chronic systemic inflammation seems to contribute. To that end, role of classical pro-inflammatory cytokines like IL-6 and TNF is better recognized, while data about IL-17 and/or IL-23 and atherosclerosis are still contradictory.\textsuperscript{3,86} It seems that except from controlling traditional cardiovascular risk factors, amelioration of systemic inflammation by bDMARD treatment plays important role in reducing cardiovascular risk in these patients. Di Minno et al. documented an important reduction of carotid intima-media thickness (cIMT) and lower number of carotid plaques, both as surrogate markers of atherosclerosis, in PsA patients treated with TNFi, in contrast to those receiving cDMARDs. In addition, treatment duration with TNFi was inversely correlated with cIMT progression, supporting the concept of accumulating anti-inflammatory impact of TNFi treatment on vascular lesions.\textsuperscript{87} In concert, Eder et al. in two cohort studies ascertained firstly that TNFi reduced the deterioration of carotid plaques, only in males. Secondly, after one year of TNFi therapy, vascular inflammation was found to be improved in both genders, regardless of traditional cardiovascular risk factors.\textsuperscript{88} The beneficial vascular effects of anti-cytokine immune therapy is correlated with improved clinical outcomes. Although data are more robust for other inflammatory arthritis, like RA, for PsA only a few studies have evaluated the effect of bDMARDs on CVD risk, let alone the potential differences among different bDMARDs and JAKinibs. A meta-analysis including only 6 studies for PsO/PsA, shown that TNFi therapy is associated with lower risk of all CVD, than the topical treatment.\textsuperscript{80} In line with these findings, another meta-analysis shown remarkable reduction of MI incidence and risk of CVD with TNFi, compared with topical therapy, phototherapy or methotrexate treatment (90). On the other hand, when other licensed bDMARs are compared with TNFi, no differences were found. In a large cohort study including 60028 patients with PsO or PsA from US, the risk for atrial fibrillation or major adverse CVD events did not diverge between groups treated with ustekinumab (IL-12/IL-23 inhibitor) or TNFi.\textsuperscript{81} As for JAK-inhibitors (JAKi), short-term safety data from OPAL Balance clinical trial, including > 650 PsA patients, do not indicate increased risk for major adverse cardiovascular events comparable to other treatment groups.\textsuperscript{82}

Mental Health Disorders
Anxiety and depression are frequent comorbidities in the setting of PsA\textsuperscript{2} and have been linked with worse clinical outcomes and lower probability of achieving disease remission.\textsuperscript{83} Although they can be owed to devastating clinical symptomatology, pain and reduced quality of life,
they are mechanistically linked with inflammatory processes and mediators like IL-6 and TNF. Data are not robust for PsA, but it seems that treatment with bDMARDs has beneficial effect also on comorbid mental health disorders. Kappelmann et al. in a meta-analysis showed that adalimumab, etanercept, infliximab and tocilizumab had beneficial effect in depressive symptomatology, in a variety of immune-mediated diseases.94 Interestingly, in a recent meta-analysis it was found that IL-12/IL-23 and IL-6 blockers demonstrated larger effects on depression occurring in immune-mediated diseases, compared to other bDMARDs.95

SAFETY

Infections

Infections are probably the most well recognised concern about the use of b- and ts-DMARDs. Overall, there are no differences for serious infections across bDMARDs and JAKinibs.96 However, a recent interim analysis of a still ongoing study (A3921133) comparing tofacitinib with adalimumab showed that serious infections were increased for JAKi in individuals aged more than 65 years old. Subsequently, EMA recommended that tofacitinib should be used in this subgroup of patients only when there is no other alternative.97 Another study analysing data from RA RCTs and CORRONA registry showed that serious infections for patients treated with tofacitinib was similar to adalimumab for 5mg twice a day (bid) dosing scheme, but higher than adalimumab for 10mg bid.98 More data will be accumulated over the next years. However, 10mg bid should be avoided in people aged over 65 years or those with an increased risk for infections.

Finally, some regimes are safer than others regarding specific infections, as outlined below.

Tuberculosis

Tuberculosis (TB) has been identified as the most common opportunistic infection among patients with autoimmune rheumatic diseases. Actually, it is well known that latent TB reactivation or de novo cases of TB are associated with TNFi treatment99,100 offering a 4-8 times higher risk. This is further increased in endemic regions for TB.101 This association could be explained having in mind the essential role of TNF-a and IFN-y for immune cells’ recruitment, phagocytosis of mycobacteria and granuloma formation.102,103 Of note, therapy with soluble TNF receptor (etanercept) is less likely to cause TB compared to anti-TNF monoclonal antibody (mAb) agents.104 Other cytokines, like interferons, IL-12, IL-17, IL-22 (105) are also implicated in immune response to mycobacterial infection. However, available data derived from clinical trials and post-marketing surveillance for IL-17-targeted agents in PsA and PsO patients suggest that the risk for TB infection/reactivation, upon treatment with these regimes is not high.106-108 Furthermore, despite the protective role of IL-12 and IL-23 against mycobacterium tuberculosis,109 no cases of active TB have been reported in PsA patients treated with ustekinumab,110,111 neither with selective anti-IL-23 mAbs.112 Finally, JAK proteins intervene in IL-12/IL-23 and IFN-y signalling113 and mutations in relevant genes are deemed to be responsible for vulnerability to mycobacterial infections.114 Studies in RA patients indicate that the incidence of TB with tofacitinib is comparable to what observed with TNFi.115 Moreover, the risk seems to parallel with higher drug doses and depends on the regional prevalence of TB. As for PsA patients, data are limited and short-term safety results from clinical trials do not report cases of TB under JAKi therapy.116 To sum up, although some regimes (eg, etanercept or IL-17/IL-23 inhibitors) might be safer than others (Figure 2), in everyday clinical practice, screening for latent TB should be recommended for all patients before initiating bDMARDs and JAKi.117

Herpes Zoster

Herpes zoster (HZ) primary infection or reactivation has been reported as an adverse event closely linked with JAKi. The underlying pathogenetic mechanisms for this are not entirely clear. However, we know that JAK-STAT pathways are integral parts of adaptive immune response to intracellular pathogens, like viruses and that JAK family proteins are involved in many steps of this virus life cycle.118 It is clear that the risk of HZ reactivation with JAKi is higher compared to bDMARDs (Figure 2). A real-world study in RA patients found approximately double incidence rate (IR) of HZ with tofacitinib compared to TNFi, abatacept, rituximab and tocilizumab. HZ reactivation in this context is mild, being usually, but not always, limited to a single dermatome.118 Risk factors augmenting the HZ reactivation risk include female sex,

Figure 2. Adverse events of bDMARDs and JAKi in PsA. Green: safe (taking into account all necessary screening procedures and prophylaxis); dark green: better safety profile compared to the others; yellow: use with caution.
age ≥65 years, concomitant or previous corticosteroid therapy (prednisolone >7.5mg per day), tofacitinib dose and Asian ancestry.\[^{119-121}\] Additionally, the risk seems to be lower in patients receiving tofacitinib-monotherapy, compared to those treated with combination therapy with cDMARDs.\[^{122}\] Finally, it is still debatable, whether some JAKi are safer than the others in terms of HZ reactivation, although this association seems to be a class effect. The risk seems to be comparable between RA and PsA patients.\[^{123}\] In conclusion, JAKi should be avoided in patients who have a past medical history of HZ infections, while it is unclear whether re-introduction of therapy with JAKi is a reasonable option after HZ reactivation.

Fungal infections
Risk for candidiasis is increased in patients receiving anti-IL-17 reagents, resulting in adjusted incidence rates of 0.4-2.2/100 patient-years.\[^{106,123}\] This is probably due to the central role of IL-17 in the defence against fungal infections.\[^{124}\] Of note, candidiasis in this setting is usually mild and does not lead to treatment discontinuation.

Malignancies
Malignancy rates in PsA receiving treatment with bDMARDs or JAKi seem to be similar to what observed in the general population, except from non-melanoma skin cancer (NMSC), which prevalence has been found to be increased. There are not observed differences across different drug categories and screening strategies are not yet defined in patients receiving bDMARDs/ tsDMARDs.\[^{117,125-128}\]

Venous Thromboembolism
Venous thromboembolism (VTE) and pulmonary embolisms (PE) are two adverse events that have been described in the context of treatment with JAKi (Figure 2). So far, data are more solid for tofacitinib, for which EMA recommended that should not be used at the 10mg bid dose for ulcerative colitis, unless there is no other option. Newer data from an interim analysis of open label trial (A3921133 study) of RA patients older than 50 years old, showed that the risk for PE was 3 and 6 times higher for tofacitinib 5 and 10mg bid, respectively.\[^{97}\] This has led EMA to recommend that tofacitinib should be used with caution for all dosing schemes and indications, when risk factors for cardiovascular or thromboembolic disease (eg, obesity, diabetes, prolonged immobility) concur. For baricitinib, data are less robust with VTEs being numerically higher in studies assessing the efficacy of this drug.\[^{129,130}\] Food and Drug administration (FDA), has approved only the lower (2mg/day) dosing scheme for rheumatoid arthritis. For other JAKi, more data are needed before we can draw a conclusion whether VTE/PE is a class effect.

Heart failure (HF)
Although biologics offer benefit in terms of cardiovascular outcomes, including myocardial infarction and cardiovascular events, severe heart failure (NYHA class III and IV) is a relative contraindication for treatment with TNFi.\[^{131}\] In a recent meta-analysis investigating the effects of various medications used in inflammatory arthritis in cardiovascular outcomes, no effect of TNFi was found on occurrence of heart failure.\[^{109}\] As the authors state though, this could be owed in a selection bias, as clinicians would avoid these regimes in patients with heart failure.

CONCLUSION
In conclusion, there are several features that can affect clinician’s decision for one or the other bDMARD. Anti-IL-17 and anti-IL-23 are better than other bDMARDs for patients with severe psoriasis, while for arthritis, enthesitis and dactylitis, no major differences are noted. IL-17 blockers should be avoided for IBD, while TNFi (except for etanercept) seem to be the better option, so far, for eye involvement. For comorbidities, evidence is still scarce, but future studies might show some benefit for some of the drugs used for PsA treatment. Safety is always a drive for choosing the appropriate treatment. Etanercept, anti-IL-17 and anti-IL-23 seem to be safer regarding TB, while HZ as well as VTE/PE should be taken into account when JAKi are prescribed. Apparently, this clinically oriented review does not disregard the phenotypic variety of PsA. Data from studies using newer technologies (eg, omics) will help to better identify subgroups within PsA and thus, guide tailor treatment approach.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
All authors contributed to drafting the manuscript.

REFERENCES
1. Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheum Dis Clin North Am 2015;41(4):545-68.
2. Fragoulis GE, Evangelatos G, Tentioulis N, Fragkiadaki K, Papoupolos S, Konstantonis G, et al. Higher depression rates and similar cardiovascular comorbidity in psoriatic arthritis compared with rheumatoid arthritis and diabetes mellitus. Ther Adv Musculoskelet Dis 2020;12:1759720X20976975.
3. Ferguson LD, Siebert S, McNees IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. Nat Rev Rheumatol 2019;15(8):461-74.
4. Gupta S, Syrini Z, Hughes DM, Zhao SS. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. Rheumatol Int 2021;41(2):275-84.
5. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391(10136):2273-84.
6. Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs 2014;74(4):423-41.
7. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I,
18. Singh JA, Guyatt G, Ogde A, Gladman DD, Dale C, Deodhar A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol 2019;71(1):5-32.

19. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol 2016;68(5):1060-71.

20. Simons N, Degboe Y, Barnetche T, Cantagrel A, Ryuissen-Witrand A, Constantin A. Biological DMARD efficacy in psoriatic arthritis: a systematic literature review and meta-analysis on articular, enthesitis, dactylitis, skin and functional outcomes. Clin Exp Rheumatol 2020;38(3):508-15.

21. McInnes IB, Baraliakos X, Deodhar A, Wüsthoff F, Mease PJ, Kavanaugh A, Ritchlin C, Nash P, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b 3 trial. Lancet 2020;395(10235):1496-505.

22. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76(1):79-87.

23. Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the Treatment of Plaque Psoriasis and Psoriatic Arthritis: A Comprehensive Review. Am J Clin Dermatol 2021:22(2):173-92.

24. Araujo EG, Engbrecht M, Hoepekens S, Finzel S, Kampylafka E, Kleyer A, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSIA) study. Semin Arthritis Rheum 2019;48(4):632-7.

25. Mourad A, Gnaideck R. Treatment of Dactylitis and Enthesitis in Psoriatic Arthritis with Biologic Agents: A Systematic Review and Metaanalysis. J Rheumatol 2020;47(1):59-68.

26. Gladman DD, Baraliakos X, Merola JF, Avila-Zapata F, et al. Adalimumab plus methotrexate versus methotrexate alone for the treatment of moderate-to-severe psoriasis: a network meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2020;79(6):700-12.

27. Schett G, Lories RJ, D’Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13(12):731-41.

28. Mease PJ, Hall GS, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med 2017;377(16):1537-50.

29. McInnes IB, Gladman DD, Deodhar A, McDonald DG, Nash P, Boehncke WH, et al. Impact of guselkumab, an interleukin-23 p19 subunit inhibitor, on enthesitis and dactylitis in patients with moderate to severe psoriatic arthritis: results from a randomised, placebo-controlled, phase II study. RMD Open 2020;6(2).

30. UNESCO. The IL-23-IL-17 pathway as a therapeutic target in axial spondyloarthritis. Nat Rev Rheumatol 2019;15(12):747-57.

31. van der Heijde D, Deodhar A, Wei JC, Drescher E, Fleishaker D, Hendrix T, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017;76(8):1340-7.

32. Whitlock SM, Eros CW, Armstrong AW, Gottlieb A, Langley RG, Lebwohl M, et al. Management of psoriasis in patients with inflammatory bowel disease: From the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2018;79(2):383-94.

33. Sibidan E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev 2020;1:CD011535.

34. Ash Z, Gajjouj-Viala C, Gossec L, Hensor EM, FitzGerald O, Wirthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2012;71(3):319-26.

35. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362(2):118-28.

36. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014;371(4):326-38.

37. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015;386(9993):541-51.

38. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017;76(3):418-31.

39. Schett G, Lories RJ, D’Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13(12):731-41.

40. Mease PJ, Hall GS, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med 2017;377(16):1537-50.

41. McInnes IB, Gladman DD, Deodhar A, McDonald DG, Nash P, Boehncke WH, et al. Impact of guselkumab, an interleukin-23 p19 subunit inhibitor, on enthesitis and dactylitis in patients with moderate to severe psoriatic arthritis: results from a randomised, placebo-controlled, phase II study. RMD Open 2020;6(2).

42. McGuire D, Tan AL, Watad A, Heilwell P. Pathophysiology, assessment and treatment of psoriatic dactylitis. Nat Rev Rheumatol 2019;15(2):113-22.

43. Vieira-Sousa E, Alves P, Rodrigues AM, Teixeira F, Tavares-Costa J, Bernardo A, et al. GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of GOLimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis. Ann Rheum Dis 2020;79(4):490-9.

44. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, You Y, Li S, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (FUSUMMIT-1/FUSUMMIT-2). Ann Rheum Dis 2016;75(11):1984-8.

45. Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. Reumatologia 2017;55(3):131-5.

46. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.
CHOOSING THE APPROPRIATE TARGET FOR THE TREATMENT OF PSORIATIC ARTHRITIS: TNF-α, IL-17, IL-23 OR JAK INHIBITORS?

Lancet 2005;366(9494):1367-74.
38. Elyoussi S, Thomas BJ, Curtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. Rheumatol Int 2016;36(5):603-12.
39. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60(4):076-86.
40. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Krahaisi M, Kiehl D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-Psa). Ann Rheum Dis 2014;73(1):48-55.
41. Rich P, Bourrier M, Soven H, Fakherzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol 2014;170(2):398-407.
42. Reich K, Sullivan J, Arenberger P, Jazayeri S, Mrowietz U, Augustin M, et al. Secukinumab shows high and sustained efficacy in nail psoriasis: 2.5-year results from the randomized placebo-controlled TRANSFIGURE study. Br J Dermatol 2021;184(3):425-36.
43. Foley P, Gordon K, Griffiths CEM, Wasfi Y, Randazzo B, Song M, et al. Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Dermatol 2018;154(6):676-83.
44. Merola JF, Elewski B, Tatulych S, Lan S, Tallman A, Kaur M. Efficacy of tofacitinib for the treatment of nail psoriasis: Two 52-week, randomized, controlled phase 3 studies in patients with moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2017;77(1):79-87 e1.
45. Sanchez-Billabo L, Martinez-Lopez D, Palmou-Fontana N, Armesto S, Gonzalez-Gay MA, Blanco R. Ab0829 Inflammatory Bowel Disease in Psoriatic Arthritis. Study of 306 Patients from a Single University Center. Prevalence, Clinical Features and Relationship to Biologic Therapy. Ann Rheum Dis 2020;79 (Suppl 1):1719-22.
46. Scarpia R, Manguso F, D’Arienzo A, D’Armiento FP, Astarita C, Mazzaeca G, et al. Microscopic inflammatory changes in colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. J Rheumatol 2000;27(5):1241-6.
47. Pugliese D, Daperno M, Forino G, Savarino E, Mosso E, Biancone L, et al. Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: An IG-ISBD study. Dig Liver Dis 2019;51(7):972-7.
48. So A, Inman RD. An overview of biologic disease-modifying anti-rheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol 2018;32(3):453-71.
49. Schreiber S, Colombel JF, Feagan BG, Reich K, Deodhar AA, McInnes IB, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. Ann Rheum Dis 2019;78(4):473-9.
50. Panes J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D’Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn’s disease: results of the phase IIb randomised placebo-controlled trials. Gut 2017;66(5):1049-59.
51. Perez-Chada LM, Merola JF. Comorbidities associated with psoriatic arthritis: Review and update. Curr Immunool 2020;214:108397.
52. Arepalli S, Rosenbaum JT. The use of biologics for uveitis associated with spondyloarthritis. Curr Opin Rheumatol 2019;31(4):349-54.
53. Bruner M, Dige A, Loff AG, Lauberg TB, Agnholt JS, Clemmensen K, et al. Spondylitis-psoriasis-enthesitis-enteroctilosis-dactylitis-ulcetis-peripheral synovitis (SPEED-UP) treatment. Autoimmun Rev 2021;20(2):102731.
54. Dick AD, Tugal-Tutun I, Foster S, Zierhut M, Melissa Liew SH, Bezyak V, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 2013;120(4):777-87.
55. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol 2019;15(3):153-66.
56. Patellas G, Dalton B, Leppanen J, Ibrahim MAA, Himmerich H. Impact of TNF-alpha Inhibitors on Body Weight and BMI: A Systematic Review and Meta-Analysis. Front Pharmacol 2020;11:481.
57. Toussirot E, Moutot L, Debecq B, Wendling D, Grandelment E, Durmoulou G, et al. TNFalpha blockade for inflammatory rheumatic diseases is associated with a significant gain in android fat mass and has varying effects on adipokines: a 2-year prospective study. Eur J Nutr 2014;53(3):561-61.
58. di Minno MN, Peluso R, Iervolino S, Lupoli R, Russoilillo A, Scarpa R, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken) 2013;65(1):141-7.
59. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2015;74(8):813-7.
60. Costa L, Caso F, Ramonda R, Del Puente A, Cantarini L, Darda MA, et al. Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. Immunol Res 2015;61(1-2):147-53.
61. Ogdie A, Palmer JL, Greenberg J, Curtis JR, Harrold LR, Solomon DH, et al. Predictors of Achieving Remission among Patients with Psoriatic Arthritis Initiating a Tumor Necrosis Factor Inhibitor. J Rheumatol 2019;46(5):475-82.
62. Hoigard P, Glintborg B, Kristensen LE, Gudbjornsson B, Love TJ, Dreyer L. The influence of obesity on response to tumour necrosis factor-alpha inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. Rheumatology (Oxford) 2016;55(12):2191-9.
63. Chehimi M, Vidal H, Eliauafar A, Pathogenic Role of IL-17 Producing Immune Cells in Obesity, and Related Inflammatory Diseases. J Clin Med 2017;6(7).
64. Pantano I, Iacono D, Favalli EG, Scalise G, Costa L, Caso F, et al. Secukinumab efficacy in patients with PsA is not dependent on patients’ body mass index. Ann Rheum Dis 2020.
65. Notario J, Deza G, Vilarasa E, Valenti F, Munoz C, Mollet J, et al. Treatment of patients with plaque psoriasis with secukinumab in a real-life setting: a 52-week, multicenter, retrospective study in Spain. J Dermatollog Treat 2019;30(5):424-9.
66. Dal Bello G, Gisondi P, Idiizlazi L, Girolomoni G. Psoriatic Arthritis and Diabetes Mellitus: A Narrative Review. Rheumatol Ther 2020;7(2):271-85.
67. Zhang C, Xiao C, Wang P, Xu W, Zhang A, Li Q, et al. The alteration of Th1/Th2/Th17/Freg paradigm in patients with type 2 diabetes mellitus: Relationship with diabetic nephropathy. Hum Immunol 2014;75(4):289-96.
68. da Silva BS, Bonfa E, da Moraes JC, Saad CG, Ribeiro AC, Goncalves CR, et al. Effects of anti-TNF therapy on glucose metabolism in patients with ankylosing spondylitis, psoriatic arthritis or juvenile idiopathic arthritis. Biologicals 2010;38(5):567-9.
69. Mantravadi S, George M, Brensinger C, Du M, Baker JR, Ogdie A. Impact of tumor necrosis factor inhibitors and methotrexate on diabetes mellitus among patients with inflammatory arthritis. BMC Rheumatol 2020;4:39.
70. Egeberg A, Wu JJ, Korman N, Solomon JA, Goldblum O, Zhao F, et al. Ixekizumab treatment shows a neutral impact on...
Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease. Arthritis Rheumatol 2018;70(3):608-16.

Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and cortico-steroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74(3):480-9.

Yang ZS, Lin NN, Li L, Li Y. The Effect of TNF Inhibitors on Cardiovascular Events in Psoriasis and Psoriatic Arthritis: an Updated Meta-Analysis. Clin Rev Allergy Immunol 2016;51(2):240-7.

Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of Ustekinumab vs TNF Inhibitor Therapy With Risk of Atrial Fibrillation and Cardiovascular Events in Patients With Psoriasis or Psoriatic Arthritis. JAMA Dermatol 2019;155(6):700-7.

Nash P, Coates LC, Knizt AJ, Meese PJ, Gladman DD, Covarrubias-Cobos JA, et al. Safety and Efficacy of Tofacitinib in Patients With Active Psoriatic Arthritis: Interim Analysis of OPAL Balance, an Open-Label, Long-Term Extension Study. Rheumatol Ther 2020;7(3):553-80.

Michelsen B, Kristianslund EK, Sexton J, Hammer HB, Fagerli KM, Lie E, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. Ann Rheum Dis 2017;76(11):1906-10.

Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 2018;23(2):335-43.

Wittenberg GM, Stylianou A, Zhang Y, Sun Y, Gupta A, Jagannath PS, et al. Effects of immunomodulatory drugs on depressive symptoms: A mega-analysis of randomized, placebo-controlled clinical trials in inflammatory disorders. Mol Psychiatry 2020;25(6):1275-85.

Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougdos M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis, Ann Rheum Dis 2020;79(6):760-70.

EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots [press release], 31 January 2020.

Winthrop KL, Citera G, Gold D, Henrhoen D, Connell CA, Shapiro AB, et al. Age-based (<65 vs ≥65 years) incidence of infections and serious infections with tofacitinib versus biological DMARDs in rheumatoid arthritis clinical trials and the US Coronra RA registry. Ann Rheum Dis 2021;80(1):134-6.

Arkema EV, Jonsson E, Baczkowsk E, Bruchfeld J, Feltelius N, Asling J, et al. Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? Ann Rheum Dis 2015;74(6):1212-7.

Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiamigli AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and anklylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 2016;15(sup1):11-34.

Seong SS, Choi CB, Woo JH, Bae KW, Jung CL, Uhm WS, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol 2007;34(4):706-11.

Bekker LG, Freeman S, Murray PJ, Ryffel B, Kaplan G. TNF-alpha controls intracellular mycobacterial growth by both inducible nitric oxide synthase-dependent and inducible nitric oxide synthase-independent pathways. J Immunol 2001;166(1):6728-34.

Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial
infected. J Immunol 2002;168(9):4620-7.

104. Tubach F, Salmon D, Ravaud P, Allonore Y, Goupille P, Breban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monobonal antibody therapy than with soluble tumor ne-
crosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 2009;60(7):1884-94.

105. Domingo-Gonzalez R, Prince O, Cooper A, Khader SA. Cytokines and Chemokines in Mycobacterium tuberculosis Infection. Microbiol Spectr 2016;4(5).

106. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, Blauvelt A, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. Arthritis Res Ther 2019;21(1):111.

107. Romiti R, Valenzuela F, Chouela EN, Xu W, Pangallo B, Moniarty SR, et al. Prevalence and outcome of latent tuberculosis in patients receiving ixekizumab: integrated safety analysis from 11 clinical trials of patients with plaque psoriasis. Br J Dermatol 2018;181(1):202-3.

108. Wu CY, Chiu HY, Tsai TF. The seroconversion rate of QuantiFERON-TB Gold In-Tube test in psoriatic patients receiving secukinumab and ixekizumab, the anti-interleukin-17A monoclonal antibodies. PLoS One 2019;14(12):e0225112.

109. Mata-Espinosa DA, Francisco-Cruz A, Marquina-Castillo B, Barrios-Payan J, Ramos-Espinosa O, Bini EI, et al. Immunotherapeutic effects of recombinant adenovirus encoding interleukin 12 in experimental pulmonary tuberculosis. Scand J Immunol 2019;89(3):e12743.

110. McInnes IB, Kavanagh A, Gottlieb AB, Puig L, Rahman P, Ritchin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382(9894):780-9.

111. Ritchin C, Rahman P, Kavanagh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73(6):960-9.

112. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2018;391(10136):2213-24.

113. Fagerli KM, Kearsley-Fleet L, Mercuri N, Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic review. Curr Med Chem 2015;22(16):1892-902.

114. Puel A, Cypowyj D, Emery P, Delichia EM, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatology (Oxford) 2019;58(5):859-68.

115. Puel A, Cypowyj S, Baverstock A, Kamurthy KL, Park SH, Gul A, Cardiel MH, Acosta PA, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. Arthritis Res Ther 2019;21(1):111.

116. Curtis JR, Xie F, Yang S, Bernatsky S, Chen L, Yun H, et al. Risk for Herpes Zoster in Tofacitinib-Treated Rheumatoid Arthritis Patients With and Without Concomitant Methotrexate and Glucocorticoids. Arthritis Care Res (Hoboken) 2019;71(9):1249-54.

117. Winthrop KL, Curtis JR, Lindsey S, Tanaka Y, Yamaoka K, Valdez H, et al. Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy. Arthritis Rheumatol 2017;69(10):1990-8.

118. Winthrop KL, Yamaoka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(10):2675-84.

119. Kivitz AJ, Cohen S, Keystone E, van Vollenhoven RF, Harauzi B, Kaine J, et al. A pooled analysis of the safety of tofacitinib as monotherapy or in combination with background conventional synthetic disease-modifying antirheumatic drugs in a Phase 3 rheumatoid arthritis population. Semin Arthritis Rheum 2018;48(3):406-15.

120. Braun J, Baraliakos X, Deodhar A, Poddbryn D, Emery P, Delichia EM, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatology (Oxford) 2019;58(5):859-68.

121. Puel A, Cypowyj S, Baverstock A, Kamurthy KL, Park SH, Gul A, Cardiel MH, Acosta PA, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. Arthritis Res Ther 2019;21(1):111.