

Recommendations for the use of biologics and other novel drugs in the treatment of psoriatic arthritis: 2017 update from the Italian Society of Rheumatology

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Abstract Objective

To update the 2011 Italian Society of Rheumatology (SIR) recommendations for the use of biologics and other novel agents in the treatment of psoriatic arthritis (PsA).

Methods

To create this new set of recommendations, the SIR "Spondyloarthritis and Psoriatic Arthritis study group – A. Spadaro" went through the following steps: literature search, identification of the items of interests for each of the four previously identified clinical domains of PsA and the different treatment phases, achievement of the consensus on all topics, and generation of the recommendations.

Results

An update on the available evidence on all of the biologics and new small molecules tested in PsA is reported, comprising the data for each of the individual articular manifestation. Indications for therapy inclusion criteria, choice of the drug, disease assessment, response definition, therapy failure management, and disease remission management for PsA peripheral joint arthritis, enthesitis, dactylitis, and spondylitis are provided. Suggestions for the treatment of patients with PsA and concomitant extra-articular manifestations are also given.

Conclusion

These evidence-based recommendations may be used for guidance in the complex and fast-evolving field of the treatment of PsA.

Key words

spondyloarthritis, anti-TNF- α , ustekinumab, secukinumab, apremilast

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Received on May 9, 2017; accepted in revised form on August 2, 2017.

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A. Marchesoni has received honoraria and speakers fees from AbbVie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, and UCB. N. Pipitone has received honoraria as a guest speaker at UCB-sponsored meetings (Immunology Summits, Prague, 2012, 2013 & 2014, MACRO Meet the expert at the Academy of Rheumatology, Bologna 13-14 April 2012, GRAPPA Workshop, Milan 29 January 2016) and Alfa-Wassermann sponsored meeting (RheWind, Bologna, Feb. 2016), he also received royalties from Uptodate.com and serves as Principle Investigator for Italy for the gevokizumab in myositis Servier study (2014), the strukumab in GCA GSK study (2016) and for the ToReMy AIFA (2017) study. S. D'Angelo has received honoraria from AbbVie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, and UCB to attend scientific meetings. A. Mathieu has received honoraria for consultations and/or presentations from AbbVie, Alfa Wassermann, Celgene, Janssen and Pfizer, and research grants from AbbVie, BMS, Pfizer and MSD. A. Cauli has received honoraria for consultations and/or presentations from AbbVie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, and UCB. L. Punzi has received grant/research support and speakers honoraria from BMS, MSD and Pfizer. R. Scarpa has received consultancy honoraria and/or research grants from AbbVie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, Roche and UCB. E. Lubrano has received consultancy honoraria and speakers fees from AbbVie, Celgene, Janssen, MSD, Novartis, Pfizer, and Sanofi-Genzyme. The other co-authors have declared no competing interests.

Background

Psoriatic arthritis (PsA) is the articular component of psoriatic disease (PD), a multi-organ disorder affecting patients with psoriasis, or with a genetic predisposition to this skin condition (1). PsA phenotypical manifestations are highly heterogeneous, in terms of both articular involvement and severity of disease. Patients with PsA may have various combinations of peripheral synovitis, dactylitis, enthesitis, and spondylitis, and each of these manifestations may vary in terms of extension, inflammation intensity, therapy response, and evolution. Therefore, the treatment of PsA should be individually tailored according to articular features, other clinical manifestations of PD, comorbidities, patient's general condition, and, last but not least, the patient's opinion. The first step for a correct therapy of a PsA patient is to have a full picture of the case, followed by a reasoned and patient-shared choice among a number of therapeutic options. There are many disease-modifying antirheumatic drugs (DMARDs) for the treatment of PsA currently available in Italy, and others will be available in the next few years. The DMARDs have been recently classified into three groups according to their pharmacological structure and mechanism of action: conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs), and biologic (bDMARDs) (2). Methotrexate (MTX), leflunomide (LEF), sulphasalazine (SSZ), and cyclosporine A (CsA) are the csDMARDs available for PsA therapy, apremilast (APR) is the only tsDMARD, the TNF-inhibitors (TNFis) [adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETA), golimumab (GOL), and infliximab (IFX)], ustekinumab (UST), and secukinumab (SEC) are the bDMARDs. IFX and ETA are also available in Italy as biosimilars. To provide guidance for the therapy of adult PsA patients, the Italian Society of Rheumatology (SIR) published its first recommendations on how to use bDMARDs in this disorder in 2006 (3), which were then updated in 2011 (4). Hereinafter, a second update, which in addition to all of the biologics includes the only tsDMARD currently available, is presented.

Methods

In 2015, the SIR appointed the steering committee of its "Spondyloarthritis and Psoriatic Arthritis study group – A. Spadaro" to update the Italian recommendations for the use of biologics in PsA. This group and other five rheumatologists with a recognised expertise in this disease, convened to agree on a strategic plan and designed the following roadmap. In order to provide a view of the current landscape as comprehensive as possible, it was decided that, in addition to the bDMARDs, also the novel non-biological drugs were to be considered. Although trials addressing the use of biosimilars in PsA have never been performed, the equivalence principle adopted by most of the regulatory agencies allows the prescription of these compounds also in this disorder, and this had to be accounted for. As both the European League against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) had just published the update of their recommendations for the treatment of PsA (5, 6), and the respective literature reviews (7-12), a further comprehensive systematic literature review (SRL) was considered unnecessary. Instead, to pick up relevant studies not included in the mentioned reviews, a search of the literature on the topic of the therapy of PsA limited to the 2014–2016 period was scheduled. This research had to be performed through PubMed for the published manuscripts and manually for the abstract presented at the 2015 and 2016 EULAR and American College of Rheumatology (ACR) meetings. Whenever possible, the recommendations were to be based on evidence. We used the well-known level of evidence developed by the US Agency for Health Care Policy and Research (AHCPR, now the US Agency for Health Research and Quality, AHRQ) (Table I) (13). The participants decided to subdivide the task force into four small subgroups, each in charge of only one of the main articular manifestations of PsA: peripheral synovitis, enthesitis, dactylitis, and spondylitis. The steps to make the recommendations were the following: evaluation of the previously published SLRs,

literature research for the period not encompassed by these reviews, indication of when to start any specific bDMARD or the tDMARD and definition of the minimal response criteria, management of the failures to bDMARDs or the tDMARD (considering lack of efficacy and toxicity independently), and management of disease remission. Given the heterogeneity of PD, it was also decided to provide the most relevant information on the effect of the various drugs in the main extra-articular manifestations in a separate section.

The recommendations generated by the four panels of experts had to be approved by the entire task force. In a modified nominal group technique, all group members were to be engaged in round-robin feedback sessions until achieving a full consensus. Finally, as the importance of the patient's point of view in the treatment decisions is widely recognised, it was decided to involve a patient representative.

Drugs for the therapy of PsA

TNF-inhibitors

Five originator compounds are currently licensed in Italy for the treatment of active PsA resistant to csDMARDs. ETA (Enbrel®), a dimeric fusion protein consisting of the extracellular portion of the human p75 TNF- receptor linked to the Fc portion of a human IgG1, is administered subcutaneously at a dose of 25 mg twice weekly or of 50 mg once a week. IFX (Remicade®), a chimerical human-murine monoclonal anti-TNF IgG1 antibody, is administered intravenously, usually at a dose of 5 mg/kg every 8 weeks. ADA (Humira®), a fully humanised monoclonal anti-TNF- α antibody, is administered subcutaneously at a dose of 40 mg every other week. GOL (Simponi®), is a human monoclonal anti-TNF- α antibody given monthly as a 50 mg subcutaneous injection. CZP (Cimzia®) is a pegylated monoclonal anti-TNF- α antibody that is administered subcutaneously at a dose of 400 mg initially and at week 2 and 4, followed by 200 mg every other week. A list of the most relevant randomised controlled trials (RCTs) on these drugs published up to December 2016 is shown in Table II.

Table I. Grading of evidence as recommended by US Agency for Health Research and Quality (AHRQ).

Source of evidence	Level of evidence	Strength of recommendation
Meta-analysis of randomised controlled trials	Ia	A or less
At least one randomised controlled trial	Ib	A or less
At least one well-designed controlled study without randomisation	IIa	B or less
At least one other type of well-designed quasi-experimental study	IIb	B or less
Well-designed non-experimental studies, such as comparative studies, correlational studies, and case studies	III	B or less
Expert committee reports or opinions and/or clinical experiences of respected authorities	IV	C

All of the TNFis, with the exception of GOL and CZP, are licensed in Italy also for the treatment of psoriasis. The efficacy data of these five TNFis on the various manifestations of PsA are reported in the specific sections.

Currently, in addition to these originators, there are two IFX biosimilars (Remsina® and Inflectra®) and one ETA biosimilar (Benepali®) that can be used in Italy to treat PsA on the basis of the equivalence principle. However, no RCT has ever studied the effects of these TNFi biosimilars in PsA.

IL-23 inhibitors

UST (Stelara®), a fully humanised IgG 1 κ monoclonal antibody that binds the common p40 subunit shared by IL-12 and IL-23, is the only IL-23 inhibitor available in Italy for the therapy of active resistant PsA. This drug is given subcutaneously at a dose of 45 mg initially at time 0 and after four weeks, and then every 12 weeks. In patients weighing 100 kg or more the recommended dose is 90 mg. The RCTs showing the effects of UST in PsA are reported in Table III. Its efficacy data on the various manifestations of PsA are reported in the specific sections. UST is also authorised in Italy for the treatment of psoriasis.

Guselkumab and tildrakizumab are two monoclonal antibodies targeting the p19 subunit of IL-23 that have shown to be highly effective in the treatment of psoriasis (39). No studies of these agents in PsA have been published so far.

IL-17 inhibitors

SEC (Cosentyx®) is a fully humanised monoclonal antibody targeting IL-17A

that has been recently licensed in Italy for the therapy of recalcitrant PsA. It is administered at a loading dose of 150 mg subcutaneously every week for five times, followed by a maintenance dose of 150 mg every four weeks. In patient failure to TNFi the recommended dose of SEC is 300 mg, with the same schedule. The most relevant RCTs examining the effects of SEC in PsA are listed in Table III. Its efficacy data on the various manifestations of PsA are reported in the specific sections. SEC is also authorised in Italy for the treatment of psoriasis.

Brodalumab, a human monoclonal antibody against interleukin-17 receptor A, has proved effective in controlling PsA manifestations in a phase II RCT (43). At present, however, the commercialisation process of this medication has been questioned because of unexpected adverse events (suicidal ideations), thus its future is uncertain.

Ixekizumab (IXE) is a recombinant humanised monoclonal antibody directed against IL-17A whose efficacy has already been proven by phase III RCTs both in psoriasis (39) and PsA (44). In the PsA trial (called SPIRIT-P1) patients naïve to biologics were randomised to receive subcutaneously IXE at 80 mg every two (n=103) or every four weeks (n=107), ADA at standard dose (n=101), and placebo (n=106). ACR20 response at week 24 was achieved by 62.1, 57.9, 57.4, 30.2% of the patients treated with IXE every two weeks, IXE every four weeks, ADA, and placebo, respectively (statistically significant differences vs. placebo). IXE at both dose regimens and ADA were also significantly more

Table II. Main RCTs of the TNFis in psoriatic arthritis.

Drug: trial acronym (ref.)	Compared drugs	Type of patients (number)	Primary end points (time)
<i>Etanercept:</i>			
na (14)	ETA 25 mg x 2 week vs. PLO	NSAID or DMARD failure (60)	PsARC (12w), radiographic score change (12m)
na (15, 16)	ETA 25 mg x 2 week vs. PLO	NSAID or DMARD failure (205)	ACR20 (24), radiographic score change (12m)
PRESTA (17)	ETA 50 mg x week vs. ETA 25 mg x 2 week	NSAID or DMARD failure (752)	Physician's global assessment of psoriasis
<i>Infliximab:</i>			
IMPACT (18-20)	IFX 5 mg/kg at week 0, 2, 6 and then every 8 weeks vs. PLO	DMARD failure (104)	ACR20 (16w), radiographic score change (50w)
IMPACT2 (21-23)	IFX 5 mg/kg at week 0, 2, 6 and then every 8 weeks vs. PLO	DMARD failure (200)	ACR20 (16w), radiographic score change (24-54w)
RESPOND (24)	IFX 5 mg/kg (after loading dose +MTX 15 mg/week vs. MTX 15 mg/week	NSAID or DMARD failure MTX naïve (105)	ACR20 (16w)
<i>Adalimumab</i>			
ADEPT (25, 26)	ADA 40 mg every 2 weeks vs. PLO	NSAID or MTX failure (113)	ACR20 (12w), radiographic score change (24w)
na (27)	ADA 40 mg every 2 weeks vs. PLO	DMARD failure (100)	ACR20
<i>Golimumab</i>			
GO REVEAL (28-31)	GOL 100 mg every 4 weeks vs. GOL 50 mg every 4 weeks vs. PLO	NSAID or DMARD failure (415)	ACR20 (14w), radiographic score change (24w)
<i>Certolizumab</i>			
RAPID-PSA (32, 33)	CZP 400 mg every 4 weeks vs. CZP 200 mg every 2 weeks vs. PLO	DMARD or TNFi failure (409)	ACR20 (12w), radiographic score change (24w)

ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab; CZP: certolizumab pegol; PLO: placebo; NSAIDs: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drug; ACR20: American College of Rheumatology 20%.

efficacious than placebo in improving dactylitis, enthesitis, and patient reported outcomes, and in reducing rate of radiographic progression. In this trial, the safety profile of IXE was similar to that reported in the psoriasis trial, with a small number of cases of oral candidiasis and neutropenia. An RCT of IXE in PsA patient with insufficient response to TNFis is ongoing.

Small molecule drugs

Small molecules are synthetic oral drugs that act at level of intracellular signalling and, as a results, modulate the release of a large number of cytokines. APR (Otezla®), a drug that specifically targets phosphodiesterase 4 (PDE4), has been recently approved in Italy for the therapy of PsA. Its recommended dose is 30 mg twice a day orally. A number of RCTs that examined this drug have been published (Table III). Its efficacy data on the various manifestations of PsA are reported in the specific sections.

Tofacitinib (TOF) is an inhibitor of the Janus-kinases (JAKs) with a strong ef-

fect on JAK-1 and JAK-3 and a weak one on JAK-2. It has been approved for the therapy of rheumatoid arthritis (RA) by the Food and Drug Administration, but in Europe its license for RA is still pending, due to safety concerns. In psoriasis TOF has proven to be very effective (54). With regard to PsA, the data of a phase III RCT recently reported at the 2016 ACR meeting (55) have shown an ACR20 response at three months of 50.5% and 60.6% for TOF 5 mg BID and 10 mg BID, respectively (significantly higher than placebo and similar to a comparison group of ADA-treated patients). In TOF-treated patients, a significant (vs. placebo) improvement was also seen in dactylitis at the dose of 10 mg BID and the 12-month radiographic progression was lower in these patients than in the placebo-treated patients (but the difference was not significant). In this study, no relevant new safety signal was recorded.

Other biological agents tested in PsA

Abatacept (ABA) is a selective T-cell co-stimulation modulator that can be

used for the treatment of RA. The efficacy and safety of this drug in PsA has been assessed by phase II RCT (56). One-hundred and seventy patients with active PsA resistant to csDMARD or TNFis were randomised (1:1:1:1) to receive placebo or ABA at doses of 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 initial doses of 30 mg/kg, followed by 10 mg/kg) on days 1, 15, and 29 and then once every 28 days. Proportions of patients achieving an ACR20 response were 19%, 33%, 48%, and 42% in the placebo, the ABA 3 mg/kg, the ABA 10 mg/kg, and the ABA 30/10 mg/kg groups, respectively. ABA induced an ACR20 response regardless of prior use of TNFis, but at 10 mg/kg the proportion of patients attaining an ACR20 response was higher in patients that had previously not been exposed to anti-TNF-α agents compared to those who had been exposed (56% vs. 31%). The safety profiles were similar among the treatment arms and comparable to those reported in studies of ABA in RA. A phase III RCTs on ABA in PsA has just been completed and its results presented

Table III. Main RCTs of ustekinumab, secukinumab, and apremilast in psoriatic arthritis.

Drug: trial acronym (ref.)	Compared drugs	Type of patients (number)	Primary end points (time)
<i>Ustekinumab</i>			
na (34)	UST 63 mg vs. UST 90 mg vs. PLO	NSAID or DMARD or TNFi failure	ACR20 (12w)
PSUMMIT1 (35-37)	UST 45 mg vs. UST 90 mg vs. PLO	NSAID or DMARD failure (615)	ACR20 (24w)
PSUMMIT2 (37, 38)	UST 45 mg vs. UST 90 mg vs. PLO	NSAID or DMARD TNFi failure (312)	ACR20 (24w)
<i>Secukinumab</i>			
FUTURE1 (40, 41)	SEC 150 mg vs. SEC 75 mg vs. PLO	NSAID or DMARD or TNFi failure (606)	ACR20 (24w)
FUTURE2 (42)	SEC 300 mg vs. SEC 150 mg vs. PLO	NSAID or DMARD or TNFi failure (312)	ACR20 (24w)
<i>Apremilast</i>			
PALACE1 (45-48)	APR 30 mg vs. APR 20 mg vs. PBO	DMARD or TNFi (<10%) failure (504)	ACR20 (16w)
PALACE2 (49)	APR 30 mg vs. APR 20 mg vs. PBO	DMARD or TNFi failure (484)	ACR20 (16w)
PALACE3 (50)	APR 30 mg vs. APR 20 mg vs. PBO	DMARD or TNFi failure (505)	ACR20 (16w)
PALACE4 (51-53)	APR 30 mg vs. APR 20 mg vs. PBO	DMARD naïve (527)	ACR20 (16w)

UST: ustekinumab; SEC: secukinumab; APR: apremilast; NSAIDs: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drug; ACR20: American College of Rheumatology 20%.

in the 2016 ACR meeting (57). At week 24, ACR20 response was achieved in 39.4% of the patients treated with subcutaneous ABA 125 mg weekly and in 22.3% of the placebo-treated patients ($p < 0.001$). ABA was also superior to placebo on radiographic progression and its safety profile was similar to placebo. Altogether these data suggest that ABA will be an effective and safe therapeutic option for patients with PsA.

Rituximab (RTX) is an anti-CD20 antibody widely used for the treatment of RA. In a small exploratory study on nine PsA patients, an ACR20 response was attained in 33% of the patients (58). As RTX might have some efficacy in PsA, the conduction of a formal RCT may be warranted.

Tocilizumab, an anti IL-6R monoclonal antibody, has been assessed in only a few patients with active PsA with contradictory results (59-61). As it might be effective in some patients, further investigation may be warranted.

Clazakizumab (CLA) is a monoclonal antibody with high affinity and specificity for IL-6. The efficacy and safety of this drug in PsA has been assessed by a phase II RCT (62). A total of 165 patients were randomised (1:1:1:1) to receive subcutaneous placebo or CLA 25 mg, 100 mg, or 200 mg every four weeks, with or without MTX. At week 16, the ACR20 response rate was significantly higher *versus* placebo only with CLA 100 mg (52.4% vs. 29.3%; $p = 0.039$). For the other doses the ACR20 response was higher in the

CLA-treated patients than in placebo-treated patients, but the difference was not significant. CLA significantly improved also enthesitis and dactylitis, with minimal improvements in skin disease. The drug was well tolerated. Despite the lack of a dose response, the results of this study seem to suggest that CLA is effective in PsA. Further studies are needed.

Safety profile of the bDMARDs and the tsDMARD registered in Italy for the treatment of PsA

TNFis
The safety data derived from the RCTs of ADA, ETA, GOL, and IFX have already been reported in the 2011 SIR recommendations on the use of biologics in PsA (4). No new safety signals for these four TNFis have emerged from the open-label extensions of their RCTs and from observational cohorts of registries. CZP, the last marketed originator TNFi, has shown a safety profile similar to that of the other TNFis (32). The well-known contraindications to TNFi therapy apply to all of them, as well as the established pre-treatment screening procedures (4). A malignancy occurrence over the previous five years is considered as one of these contraindications, and the summary of product characteristics (SPC) of all of the TNFis warn against using the drug in these cases. However, many experts in biologic therapy argue that, after more than 15 years of TNFi use, there is enough evidence to think that these

drugs are safe in patients with a previous cancer. For PsA, robust data on this issue are still lacking, but it is worth mentioning that in patients with psoriasis treated with TNFis the risk of malignancy and of progression of previous malignancy is not significantly higher than in non-treated patients (63). In our opinion, in patients with severe active PsA not responsive to other therapies, the beneficial effects of TNFi therapy are likely to outweigh the risk of malignancy. Accordingly, in selected cases of PsA patients with a previous malignancy, TNFis might be used (strength of recommendation: C). Decision shared with the patient, permission of the oncologist, and oncologic follow-up are the mandatory requisites for this therapeutic approach.

Ustekinumab

In the two main RCTs of UST, rate and severity of adverse events (AEs) were similar in the study therapy groups and in the placebo groups (35, 38). During two years of follow-up, the rate of AEs remained consistent with that previously recorded in the UST arms; severe infections were very uncommon, no cases of active TB or demyelinating diseases were reported, and the number of malignancy and major cardiac events (MACEs) was very low, (64). In an international registry with a huge number of patients with psoriasis (PSOLAR: Psoriasis Longitudinal Assessment and Registry), the rate of serious infections and malignancies

was lower in the UST-treated patients than in the patients treated with ADA, IFX, ETA, and MTX (65). In a meta-analysis performed in psoriatic patients, UST was the only bDMARDs that did not show increased risk of AEs compared with placebo (66). No particular safety or tolerability issues have emerged from all these studies. Previous malignancy is not an absolute contraindication to the use of UST in PsA, but the SPCs of this drug warn against the possible association between cancer and immunosuppressive therapy. In our opinion, on the basis of the PSOLAR data, patients with previous malignancy may be treated with UST with appropriate caution (strength of recommendation C)

Secukinumab

In the FUTURE 1 and 2 trials, the rate of AEs and serious AEs in the SEC-treated patients was comparable with that of the placebo-treated patients (40, 42). Upper respiratory tract infections and nasopharyngitis were the most common AEs (72 and 49 per 100-patient years, respectively). No cases of TB and demyelinating diseases were reported. Overall, in the these two RCTs, there were 17 cases of neutropenia across the entire treatment period, all mild and often transient. Due to its mechanism of actions, some concerns have been raised on the development of mucosal mycosis during SEC therapy. In FUTURE 1 and 2, three and two patients treated with SEC (0.7%) developed *Candida* infections, respectively, compared with no patient in the placebo groups. De novo Crohn's disease occurrence, another postulated AE of SEC therapy, was seen in only one patient treated with this drug. Among SEC-treated patients, incidences of MACEs and malignancy were low and no suicidal ideation was reported. In a meta-analysis of 10 phase II and phase III RCTs on psoriasis, the safety of SEC (3,430 patients) was compared with that of ETA (563 patients) over a 52-week period (67). The exposure-adjusted incidence rates of AEs were comparable across treatments. Non-serious skin/mucosal *Candida* infections were more frequent in the SEC-treated

patients than in the ETA treated patients, especially with the 300 mg dose. Overall, the available data suggest that safety and tolerability of SEC is at least comparable with that of TNFis, probably with less concerns for TB and demyelinating conditions. Attention should be paid to skin/mucosal *Candida* infections. Although the initial concern about possible exacerbations of underlying Crohn's disease has not been confirmed by more robust data (68), it is not advisable to use this drug in patients with PsA and concomitant Crohn's disease. As for previous malignancy, there is insufficient experience to provide an indication on this issue.

Apremilast

The safety profile of APR emerging from the four RCTs (48-53) of the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) program has been the subject of a meta-analysis, which showed that the number of serious AEs in the APR groups was comparable with that of the placebo groups (69). Mild nausea and diarrhea were the AEs more frequently associated with APR. These side effects were seldom responsible for drug discontinuation (<2%) and they usually resolved after a few weeks without dose modifications. Headache was also recorded in a minority of APR-treated patients. An intriguing effects associated with APR use was weight loss. Patients treated with this drug lost a mean of about two kilos and about 17% of them experienced a reduction in body weight greater than 5%. This effect was not related to nausea or diarrhoea. Safety data pooled from PALACE 1, 2, and 3 are available through week 156 (70). No increase of AEs was observed during this follow-up period. In addition, no new case of TB was recorded, the rate of malignancy, MACEs, and serious infections was very low, and virtually no patients had serological abnormalities. For this reason, no serological test is required before and during APR therapy. All these data suggest a favourable safety and tolerability profile for APR. As for previous malignancy, there are insufficient data to provide an indication on this issue.

General inclusion criteria for treatment with bDMARDs or the tsDMARD

To be eligible for treatment with bDMARDs or the tsDMARD, patients should have active or aggressive PsA diagnosed by a rheumatologist with expertise in this disease. CASPAR classification criteria (71) should be used in addition to clinical judgement. Psoriasis should preferably be diagnosed by a dermatologist. The predominant articular feature should guide the choice of the therapy, but all of the articular and extra-articular manifestations presented by the patient should be taken into account. The importance of a comprehensive approach to the patient with PsA has emerged as a key factor also by a recent survey performed in a group of Italian rheumatologists (72). The definitions of active and aggressive disease and the treatment recommendations for each of the articular domain of PsA have been reported in the specific sections.

Therapy with TNFis is contraindicated in the following conditions: sepsis or high risk of developing sepsis, active infections, including TB, hepatitis B virus (HBV), human immunodeficiency virus, latent TB not adequately treated, heart failure class III or IV according to the New York Heart Association, and demyelinating disorders. Malignancies over the last five years are still considered a contraindication to the use of TNFis. However, as discussed in the safety section, exceptions to this rule might be possible. Heart failure class III or IV and demyelinating disorders are not reported contraindications to the use of UST, SEC, and APR. For the latter of these drugs, also latent TB and HBV infection are not a contraindication to its use. In contrast, in patients with sepsis or high risk of developing sepsis and active infections also UST, SEC, and APR cannot be used.

According to all this, the well-known screening procedures should be applied for all of the bDMARDs but not for APR. For any pregnancy-related issue we recommend to follow the indications of the SPCs of each drug. It is worth mentioning, however, that the British Society for Rheumatology has indicated that, in contrast to the other

Table IV. Summary of the SIR recommendations on the use of bDMARDs and tsDMARDs in psoriatic arthritis.

	Peripheral joint arthritis	Enthesitis	Dactylitis	Spondylitis
Inclusion criteria	1. ≥ 1 inflamed joint 2. no response to NSAIDs, local steroid injections, csDMARDs 3. favourable expert's opinion based on subjective and objective measurements	1. \geq inflamed enthesis 2. no response to NSAIDs or local steroid injections 3. favourable expert's opinion based on patient-centred evaluation	1. \geq acute dactylitis 2. no response to NSAIDs or local steroid injections 3. favourable expert's opinion based on patient-centred evaluation and on presence of joint damage	1. active spondylitis (BASDAI ≥ 4) 2. no response to 2 NSAIDs (for 4 weeks) 3. favourable expert's opinion based on subjective and objective measurements
Choice of the drug	TNFis, SEC, UST, APR. Decision based on multiple factors. No APR if erosive disease	TNFis, SEC, UST, APR. Decision based on multiple factors	TNFis, SEC, UST, APR. Decision based on multiple factors	TNFis, SEC. UST if others contraindicated. Decision based on multiple factors
Definition of response	1. DAPSA score ≤ 4 ; if not feasible ACR50 or MDA or DAPSA ≤ 14 2. favourable expert's opinion	1. absence of enthesitis; if not feasible, pain-VAS ≤ 15 , or PGA-VAS ≤ 20 or HAQ-DI ≤ 0.5 , or MDA criteria. 2. favourable expert's opinion	1. absence of dactylitis; if not feasible, pain-VAS ≤ 15 , or PGA-VAS ≤ 20 or HAQ-DI ≤ 0.5 , or MDA criteria. 2. favourable expert's opinion	1. remission (by clinical judgement) or $\geq 50\%$ or ≥ 2 -point BASDAI improvement 2. favourable expert's opinion
Therapy failure	A. TNFi primary lack of efficacy: swap or switch B. TNFi secondary loss of efficacy: switch. C. TNFi adverse event: swap if class effect, otherwise switch D. bDMARDs other than TNFis and APR failure: swap	A. TNFi primary lack of efficacy: swap or switch B. TNFi secondary loss of efficacy: switch C. TNFi adverse event: swap if class effect, otherwise switch D. bDMARDs other than TNFis and APR failure: swap	A. TNFi primary lack of efficacy: swap or switch B. TNFi secondary loss of efficacy: switch C. TNFi adverse event: swap if class effect, otherwise switch D. bDMARDs other than TNFis and APR failure: swap	A. TNFi primary lack of efficacy: swap or switch. B. TNFi secondary loss of efficacy: switch C. TNFi adverse event: swap if class effect, otherwise switch D. SEC failure: swap to a TNFi
Management of remission	Remission ≥ 6 months: TNFi dose reduction of 1/3 and then after 3 months of 1/2 the initial dose.	Remission ≥ 6 months: dose reduction of 1/2 the initial dose. Withdrawal possible after ≥ 3 months of dose reduction	Remission ≥ 6 months: dose reduction of 1/2 the initial dose. Withdrawal possible after ≥ 3 months of dose reduction	Remission ≥ 6 months: cautious dose reduction

bDMARDs: biologic disease-modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; BASDAI: Bath Ankylosing Spondylitis Activity Index; TNFis: TNF inhibitors; SEC: secukinumab; UST: ustekinumab; APR: apremilast; DAPSA: disease activity psoriatic arthritis; ACR50: American College of Rheumatology 50%; MDA: minimal disease activity; VAS: visual analogue scale; PGA: patient global assessment; HAQ: Health Assessment Questionnaire.

TNFis, CZP might be compatible with all the three trimesters of pregnancy (73). Recent experimental data seem to confirm this suggestion (74).

Finally, prior to start a therapy in patients with PsA, we strongly recommend to share all decisions with the patient, who should be comprehensively informed on any relevant aspect related to the therapy.

A summary of the recommendations for each articular domain of PsA is presented in Table IV.

Peripheral joint arthritis

TNFis

TNFis have all unequivocally shown clinical efficacy on peripheral synovitis in PsA, both in naïve and csDMARD failure patients (level of evidence Ia) (7, 8, 75). They have also demonstrated to be better than placebo (level of evidence Ia) and MTX (level of evidence Ib) on

radiographic progression (76, 77). The efficacy and safety data of ADA, ETA, IFX, and GOL in the treatment of psoriatic peripheral synovitis have already been described (4). A brief summary of these data and of data from more recent studies is reported.

The pivotal trial on ADA (Adalimumab Effectiveness in Psoriatic Arthritis Trial [ADEPT]) (25) showed that, at week 24, 57%, 39% and 15% of the ADA-treated patients achieved respectively ACR20, ACR50 and ACR70 responses, compared with 15%, 6% and 1% of the placebo-treated patients. ADA was also more effective than placebo in inhibiting radiographic progression. In the open-label extension of this study, at week 104 the effects on clinical response and radiographic progression were retained in most patients (26). An open-label study confirmed the effectiveness of ADA in patients with active PsA who

were refractory, or intolerant, to at least two csDMARDs, one of which had to be MTX (78).

In its pivotal RCT, at week 12, ETA demonstrated an ACR20 response of 59% compared with 15% in the placebo group (15) and these results were maintained at week 24. In addition, at month 12, the radiographic progression was significantly inhibited by ETA and this result was sustained after two years (16). The efficacy of ETA has been confirmed by the Psoriasis Randomised Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) where 50 mg twice a week of this drug was compared with 50 mg weekly, with psoriasis improvement as primary endpoint (17). The higher dose led to a faster reduction in the skin involvement but no difference was noted in the arthritis amelioration.

Two RCTs (IMPACT [Infliximab Multinational Psoriatic Arthritis Controlled

Trial] and IMPACT2) have established efficacy and safety of IFX in PsA (18, 21). In the IMPACT study, at week 12, the ACR20, 50, and 70 responses were 65%, 46%, and 29%, respectively, in the IFX group, and 10%, 0%, and 0% in the placebo group. Radiographic progression was significantly lower in the IFX-treated patients. The efficacy was maintained through the two-year extension of the study. IMPACT2 yielded similar results.

A RCT (GO-REVEAL) demonstrated the clinical efficacy and safety of GOL in patients with active PsA (28). In this study, at week 14, 51% of patients receiving GOL 50 mg every four weeks and 45% of patients receiving GOL 100 mg achieved an ACR20 response, compared with 9% of the placebo-treated patients. GOL was also superior to placebo in controlling radiographic progression. These results were all retained after two and five years (30, 31).

CZP is a TNFi recently commercialized in Italy for the treatment of active PsA. Its efficacy and safety has formally been assessed in a RCT (RAPID-PsA) (32). Unlike the RCTs of the other TNFis, in the RAPID-PsA up to 40% of patients could be TNFi failure for reasons other than lack of efficacy. The enrolled patients were randomised 1:1:1 to placebo, 200 mg CZP every 2 weeks (Q2W) or 400 mg CZP every 4 weeks (Q4W) for a time period of 24 weeks. The primary endpoints of the study were ACR20 response at week 12 and modified Total Sharp Score change from baseline at week 24. ACR20 response was significantly greater in CZP 200 mg Q2W and 400 mg Q4W-treated patients than in placebo-treated patients (58% and 52% vs. 24%) at week 12. Similarly, ACR50 responses were observed in 44% and 40% of patients treated with CZP Q2W and Q4W, respectively, versus 13% of those receiving placebo, while ACR70 responses were recorded in 26% and 24% of patients in the CZP Q2W and Q4W arms versus 4% in the placebo arm. All differences in ACR responses were significant. There was also a statistically significant improvement in physical function from baseline, measured by HAQ-DI in CZP patients compared with placebo patients (-0.50

vs. -0.19). Higher ACR response with CZP was independent of prior TNFi exposure. Likewise, concomitant csDMARD use did not affect response to CZP. After correction of an unbalanced imputation method, the radiographic progression resulted significantly lower in the CZP than in the placebo patients (33). In the 96-week extension of the RAPID-PsA, ACR responses were maintained, regardless of prior TNFi exposure. Placebo patients switching to CZP experienced rapid clinical improvements, which was maintained to week 96. No progression of structural damage was observed over the 96-week period. Overall these data indicate that CZP efficacy in psoriatic peripheral synovitis is comparable with that of other TNFis.

IL-23i

The efficacy of UST in abating signs of peripheral joint inflammation in PsA has been first proven by a relatively small RCT (34) and then confirmed by two robust studies (35, 38) (level of evidence Ib).

In the PSUMMIT 1 trial, adult patients with active PsA resistant to NSAIDs or csDMARDs were randomly assigned (1:1:1) to 45 mg UST, 90 mg UST, or placebo at week 0, week 4, and every 12 weeks thereafter. At week 24, 42% of patients treated with UST 45 mg, 50% of those treated with UST 90 mg, and 23% of the placebo patients achieved an ACR20 response. Similarly, ACR50 was obtained in 25%, 28% and 9% of patients, respectively, and ACR70 was achieved in 12%, 14%, and 2% of patients, respectively. All of these differences between UST and placebo were statistically significant. Clinical responses were maintained through week 52. In the PSUMMIT 2 trial, patients with active PsA despite previous therapy with NSAIDs or csDMARDs or TNFis (at least half of them) were randomised to UST 45 mg or 90 mg or placebo at week 0, week 4, and then every 12 weeks. At week 24, the ACR 20 responses were 44%, 44%, and 20% in the 45 mg, 90 mg UST-treated patients and in the placebo-treated patients, respectively. The more stringent ACR50 response occurred in 17% (UST 45

mg), 23% (UST 90 mg), and 7% (placebo) of the treated patients. All of these differences between UST and placebo were statistically significant. Numerical but not significant differences were observed for ACR70 response. These results were sustained through week 52. Interestingly, a sub-analysis showed that ACR20 responses to UST were more pronounced in TNFi-naïve patients (54%) than in TNFi-experienced patients (36%). The effect of UST on radiographic progression was studied by pooling the populations of PSUMMIT 1 and PSUMMIT 2 trials (38). UST-treated patients demonstrated significantly less radiographic progression at week 24 than placebo recipients. From week 24 to week 52, inhibition of radiographic progression was maintained for UST-treated patients, and progression was substantially reduced among initial placebo recipients who started UST at week 16 or week 24. These data indicate that UST (regardless of the dose) can inhibit radiographic progression of peripheral joint damage in active PsA (level of evidence Ib).

IL-17i

After a phase II proof-of-concept RCT (79), the efficacy of SEC in improving peripheral psoriatic synovitis and reducing radiographic progression has been established by two phase III RTCs (40-42) (level of evidence Ib). The FUTURE 1 trial enrolled patients with active PsA despite previous treatment with NSAIDs or csDMARDs or TNFis (less than 30%). Patients were randomised in a 1:1:1 ratio to receive either an intravenous dose of SEC of 10 mg/kg at baseline and weeks 2 and 4, followed by subcutaneous SEC at a dose of either 150 mg or 75 mg every 4 weeks, or placebo. At week 24, the ACR20 response was significantly higher among patients receiving SEC at either the 150 mg (50%) dose or the 75 mg dose (50%) than among those receiving placebo (17%). ACR50 and ACR70 response was obtained in 31% (SEC75), 35% (SEC150), 7% (placebo) of patients, and in 17% (SEC75), 19% (SEC150), 2% (placebo) of patients, respectively. All of these differences were statistically significant. In this study ra-

diographic progression was significantly lower in SEC-treated patients over 52 weeks of treatment. In the FUTURE 2 trial patients with PsA resistant to NSAIDs or csDMARDs or TNFis were randomised in a 1:1:1:1 ratio to receive subcutaneous SEC 300 mg, 150 mg, 75 mg or placebo once a week from baseline to week 4 and then every 4 weeks. At week 24, in the SEC-treated patients the ACR20 responses were 54% (300 mg), 51% (150 mg), and 29% (75 mg), while in the placebo patients it was 15%; ACR50 responses were 35%, 35%, 18%, and 7%, respectively. All these differences were statistically significant. The ACR70 response, which was considered an exploratory endpoint, was reached in 20%, 21%, 7% of patients treated with SEC 300, 150, 75 mg, respectively, and 1% of patients treated with placebo. In this study, a sub-analysis on the patients failure to TNFis showed that the ORs for SEC to achieve an ACR20 response as opposed to placebo was statistically significant for the 300 mg dose only. The clinical efficacy of SEC 300 mg and 150 mg was maintained through week 52.

PDE4i

APR is the only oral small molecule licensed in Italy for the treatment of PsA. A first phase II RCT (80) and several subsequent RCTs have demonstrated that this drug is superior to placebo in reducing peripheral joint inflammation in PsA (45-54) (level of evidence Ib). In the PALACE 1 trial, PsA patients with active disease despite prior therapy with csDMARDs or TNFis ($\leq 10\%$ of the enrolled patients) were randomised 1:1:1 to APR 30 mg twice a day or APR 20 mg twice a day or placebo, stratified by baseline DMARD use (yes/no). At week 16, the ACR20 responses were 31% for APR 20 mg, 40% for APR 30 mg, and 19% for placebo. ACR50 and ACR70 responses, evaluated at week 24, were, respectively, 15% and 5% in the APR 20 mg group, 20% and 11% in APR 30 mg group, and 4% and 1% in the placebo group. All these differences were statistically significant. Biologic-naïve patients generally experienced higher absolute ACR20 response rates compared with biologic-experienced

patients. The open-label extension of this study showed a maintained efficacy over 104 weeks. These results were confirmed by the PALACE 2 and PALACE 3, two trials with the same design as PALACE 1. In the former study, the 16-week ACR20 response was achieved by 37%, 32%, and 19% of the patients treated with APR 20 mg, APR 30 mg, and placebo, respectively. In the latter trial this level of response was attained by 28% (APR20 mg), 40% (APR 30 mg), and 18% (placebo) of patients. This improvement was sustained through week 52. No data on inhibition of radiographic progression are currently available for APR.

Inclusion criteria

Therapy with bDMARDs or the tsDMARD should be considered in patients with PsA predominantly characterised by peripheral arthritis if:

1. They have at least one inflamed joint.
A joint is considered inflamed if it is tender, painful, and swollen (excluding “bony” swelling only, which may be due to structural damage in the absence of active synovitis).
2. They have not responded to NSAID therapy and to at least one of the csDMARDs used in PsA (in order of preference: MTX, SSZ, LEF, and CsA), administered alone or in combination for at least three months (at full therapeutic or tolerated doses unless contraindicated). We consider “full therapeutic doses” 15–25 mg per week for MTX, 2–3 grams per day for SSZ, 20 mg per day for LEF, and 3 mg per kg/body weight per day for CsA. Patients with monoarthritis or oligoarthritis should also have failed at least two glucocorticoid (GC) local injections.
3. According to the expert’s opinion, they are suitable for a therapy with biologics. This opinion should be based on pain and global disease activity reported by the patient on a 10 cm visual analogue scale (VAS), 1-hour erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) serum level, and radiographic findings. Suitable composite indices can be used as an aid in this decision. In our opinion the Disease Ac-

tivity PSoriatic Arthritis (DAPSA) (81) index is the most practical in a clinical setting. A DAPSA value >14 and ≤ 28 is considered indicative of moderate disease activity and >28 of high disease activity.

Patients may also be considered for bDMARD therapy if they develop new joint deformities or new erosions or worsening of pre-existing erosions consistent with PsA on conventional x-rays, even if they have an acceptable clinical response to their treatments. In this respect, we recommend in patients with polyarticular PsA to take radiographs of the involved joints once a year. If available, power-doppler ultrasound (PDUS) may be used to evaluate synovitis activity and joint damage. Patients with very active (≥ 5 swollen joints and elevated inflammatory indices) and aggressive (anatomical joint damage) disease should be treated with bDMARDs as soon as possible. In this regard, it is worth mentioning that in patients with PsA a treat-to-target strategy might yield better outcomes than a standard therapy (82) (level of evidence IIa).

Choice of drug

TNFis, UST, SEC, and APR may all be used as first line agents to treat active peripheral joint arthritis of PsA resistant to csDMARDs (strength of recommendation A). APR should not be used in case of erosive disease (strength of recommendation C). The choice should be based on other articular features, extra-articular manifestations, global health status, patient’s preference, safety data, physician’s confidence with the drugs, and costs. For the sake of cost-reduction, when IFX and ETA are indicated, the licensed biosimilar products rather than the originators could be used.

Data from registries and from small studies suggest that concomitant csDMARDs may lead to a higher survival rate and to a better efficacy of TNFi therapy, especially when using monoclonal antibodies (83, 84). However, a recent SLR on this issue did not find differences between TNFi monotherapy and add-on MTX therapy in patients with PsA (82). Given the lack of data, whether to combine a bDMARD with

a csDMARD should be decided on an individual basis by rheumatologists expert in PsA management.

Monitoring of disease activity

The target of the therapy should be the remission, that is a complete disappearance of any symptom and sign of peripheral synovitis. If remission is not feasible, a state of residual low disease activity is considered acceptable. The first assessment should be performed after three months of therapy. As the definitions of disease activity states of the DAPSA have recently been provided (81), and given the simplicity of this score, we suggest this index to monitor the state of activity of peripheral synovitis. The DAPSA encompasses counts of tender (n=68) and swollen (n=66) joints, patient's evaluation of pain and global disease activity on VAS, and CRP (mg/dl) serum level. A DAPSA value ≤ 4 is considered indicative of remission, >4 and ≤ 14 of low disease activity. DAPSA changes of 50/75/85%, reflects minor, moderate and major improvement, respectively. Alternatively, in patients with psoriatic polyarthritis (≥ 5 affected joints), the ACR response criteria with a 66/68 joint count can be used to assess the response to the therapy. Finally, the Minimal Disease Activity (MDA) is another useful tool to classify patients as responder to therapy (85). According to this index, a state of low disease activity is reached whether five of the following seven criteria are met: number of tender joints (68 count) ≤ 1 , number of swollen joint (66 count) ≤ 1 , PASI (Psoriasis Area Severity Index) ≤ 1 or BSA (Body Surface Area) ≤ 3 , patient pain on VAS ≤ 15 , patient global activity on VAS ≤ 20 , HAQ-DI (Health Assessment Questionnaire-Disability Index) ≤ 0.5 , tender enthesal points ≤ 1 . Patients are considered responders to the therapy if the following two conditions are satisfied:

1. Achievement of remission (DAPSA score ≤ 4) or, if not feasible, low disease activity (defined by DAPSA ≤ 14 or ACR50 criteria or MDA).
2. Expert's opinion that a good response has been achieved and, therefore, that the therapy should be continued.

Patients who meet these criteria at three months should be clinically reassessed at six months and subsequently every four-six months. Patients that do not meet them after three months of therapy should be considered treatment failures. However, if in the expert's opinion at least a partial but meaningful clinical improvement has occurred within the first three months, treatment may be continued for a further three months, and patients reassessed after that period of time.

Management of patients who fail a bDMARD or APR

The availability of drugs with different mechanisms of action (MOA) opens the choice between switching from a TNFi to another one or swapping from a MOA to a different one. In the RAPID-PsA RCT about 20% of the patients starting CZP had previously failed another TNFi. The response rates between TNFi-naïve and TNFi-experienced were comparable, but the number of patients previously treated with a TNFi was small and primary failures were excluded from the study. Most of the data on TNFi switching in patients with PsA come from registries (86-88). These data showed that the second TNFi was less efficacious than the first and the third less than second (level of evidence II). All of RCTs on the new drugs with a different MOA (APR, SEC, UST) included patients insufficient responder (IR) to a TNFi. The response rates of these patients were significantly higher in those taking the study therapy than in those treated with placebo, but lower in the TNF-IRs than in the TNF-naïves. There are no data about swapping from drug with new MOAs to TNFis.

On the basis of these observations and our judgement we suggest the following strategies for the following scenarios (strength of recommendation B).

- A. TNFi failure due to primary lack of efficacy: swapping to another MOA or switching to another TNFi.
- B. TNFi failure due to secondary loss of efficacy: switching to another TNFi.
- C. TNFi failure due to adverse event: if the adverse reaction is likely to be a class effect, swapping to another

MOA, otherwise switching to another TNFi.

D. bDMARDs other than TNFis and APR failure: there is no alternative to swapping to another MOA.

The choice of the therapy should also be based on the global clinical picture of the patient (development or worsening of extra-articular manifestations, other comorbidities).

Patients who meet the clinical response criteria but develop new anatomic joint damage may be considered for treatment with another bDMARD. All of the bDMARDs are effective in reducing the rate of radiographic progression in PsA (level of evidence Ia for TNFis and Ib for drugs with other MOAs). These data, however, are referred to the erosive damage only. No RCT has ever evaluated the impact of the various biologics on the damage due to new bone apposition, a typical feature of PsA. Personal experience and data from ankylosing spondylitis seem to suggest that TNFis are poorly effective in controlling this type of bone damage (level of evidence 4). Specific studies on this issue are needed.

There are insufficient data to establish whether add-on MTX can further reduce joint structural damage in PsA patients taking bDMARDs. The only weak evidence comes from the 5-year extension of the GO-REVEAL study, where concomitant MTX inhibited radiographic progression more than GOL alone (31). Therefore, we do not recommend concomitant MTX in case of joint damage progression despite good clinical response with bDMARD therapy (strength of recommendation C).

How to manage disease remission

Clinical remission may be defined as a persistent state of disappearance of any symptom and sign of peripheral synovitis. Clinical remission accompanied by the absence of any new joint damage defines a state of complete synovitis remission. As metric surrogates of clinical remission we suggest the DAPSA definition (score ≤ 4) or the state of deep disease control of the MDA, recently indicated as the fulfillment of all of the seven criteria of this index (89).

Patients in clinical remission for at least

six months and no joint damage progression might be candidate for dose reduction or withdrawal of the therapy. However, standardised clinical trials specifically addressing this issue have never been performed and case-control and observational studies have provided conflicting results. In an observational study published some years ago, remission defined as absence of any clinical manifestation was achieved by 24% of 236 PsA patients (more frequently with TNFi) and lasted for a mean period of 24 ± 2.4 months (90). In a case-control study, in 76 PsA patients treated with ADA, remission (defined as above) was achieved by 79.6% of the patients and, after spacing ADA dose to 40 mg every four weeks, it was maintained by 88.6% of these patients over a mean follow-up period of 28.9 ± 8.4 months (91). A more recent observational study on only 26 PsA patients (12 on TNFis) in clinical remission (absence of any clinical articular manifestation) showed a relapse rate of 76.9% over a mean period of 74.5 ± 51.7 days after treatment discontinuation (92). In a retrospective study, 18% of 83 PsA patients taking TNFis who had achieved remission ($\text{DAS28} \leq 3.2$) underwent dose reduction by one-third. Remission was maintained in 60% of these patients over a mean follow-up period of 1.0 ± 0.8 years (93). Another retrospective study on 141 PsA patients in MDA with ADA or ETA therapy, showed that the interval between injections could be extended in 46.1% of the patients without provoking relapses (94). On the basis on this data, in our opinion, in patients with arthritis in remission for at least six months TNFi dose-reduction of one-third, and then after three months of half the initial dose, might be tried (strength of recommendation C). In contrast, therapy withdrawal is not advisable (strength of recommendation C). Patients should be informed about risks and benefits of treatment reduction, and they should be actively involved in this decision. Patients that after a therapy modification show signs of arthritis relapse must immediately go back to the full dose of TNFi. As no data exist on therapy reduction or discontinuation in PsA patients treated with drugs other

than TNFis, we do not recommend this strategy be applied in daily practice (strength of recommendation C).

Enthesitis

TNFis

In the ADEPT study it was reported that ADA was non-significantly more effective than placebo on enthesitis but data were not presented (exploratory endpoint) (25). In a smaller RCT, at week 12, ADA therapy reduced the enthesitis score more than placebo treatment but the difference was not significant (27). Two observational studies showed an improvement of enthesitis with ADA but there was no placebo comparison arm (level of evidence 3) (73, 95). Similarly, enthesitis was not a study endpoint in ETA RCT and even if in the PRESTA trial this disease feature responded to ETA, this result was impaired by the lack of a placebo control group (level of evidence 3) (15, 17). In the IMPACT and IMPACT2 studies, the percentages of patients with enthesitis after treatment was significantly smaller for IFX as opposed to placebo (14% vs. 31%, $p=0.02$ and 20% vs. 37%, $p=0.002$, respectively) (level of evidence Ib) (18, 21). In the GO-REVEAL trial, at week 12 patients treated with GOL 50 or 100 mg experienced a 50% median improvement of a PsA-modified MASES score versus 0% of the placebo patients ($p<0.001$) (level of evidence Ib) (28). In the RAPID-PsA RCT, Leeds Enthesitis Index (LEI) mean change at week 24 was -2.0 for CZP 200 mg every two weeks, -1.8 for CZP 400 mg every other week, and -1.1 for placebo (differences statistically significant) (level of evidence Ib) (32). Overall, despite the lack of proper data on the efficacy of ADA and ETA on enthesitis, the solid evidence derived from the other TNFi RCTs suggests that TNFis are effective on enthesitis as a class.

IL-23i, IL-17i, and PDEi

In PSUMMIT1, at week 24 the percentage of patients with enthesitis was significantly lower in the UST 45 mg (69%) and UST 90 mg (61%) groups than in the placebo group (81%) (36). In PSUMMIT2, where most of the par-

ticipants were TNFi-experienced, the percentages were 70% and 76% for UST 45 and 90 mg, respectively, and 88% for placebo (differences statistically significant) (37). In both these RCTs, at week 24 a PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) score improved more in the UST-treated than in the placebo-treated patients, but the difference was statistically significant only for UST 90 mg in PSUMMIT1.

In FUTURE1, at week 24, resolution of enthesitis was seen in 47.5% of the patients in the SEC 150 and 75 mg combined group as opposed to 12.8% of the patients in the placebo group (difference statistically significant) (40). In FUTURE2, at week 24, enthesitis disappeared in 40% of the patients treated with SEC (pooled data for all doses) versus 22% of the placebo-treated patients, but the statistical significance of this difference was not tested because an endpoint higher in the hierarchy method used in the study (PASI75 for SEC 75 mg) had not been reached (42). In PALACE1, at week 24, a MASES of 0 was achieved by a significantly greater proportion of patients treated with APR 20 mg (32%) and APR 30 mg (33.6%) versus patients treated with placebo (4.4%) (46). The mean reduction in the MASES was significantly higher only in the APR 30 mg group. Altogether, the data of all of these RCTs indicate that UST, SEC, and APR are efficacious in improving enthesitis due to PsA (level of evidence Ib).

Inclusion criteria

Therapy with bDMARDs or the tsDMARD should be considered for PsA enthesitis if:

1. At least one enthesial site is inflamed. An enthesitis is considered inflamed if it is painful and tender and other possible causes are reasonably excluded. When available, PDUS may help distinguish true enthesitis from enthesopathy.
2. Treatment with NSAIDs and local GC injections have proven ineffective (Achille's tendon should not be treated with GC local injections because of the risk of tendon rupture; it is generally believed that GC injec-

tions in the corresponding bursa do not bear this risk) (strength of recommendation C).

3. According to the expert's opinion, a therapy is indicated. This opinion should be mainly based on patient's evaluation of quality of life and/or pain. Suitable instruments for this evaluation, such as HAQ-DI, 10-cm VAS for pain, and 10-cm VAS for disease global activity, should be used.

As enthesitis usually does not lead to irreversible anatomic damage, in patients with this manifestation resistant to NSAIDs and GC injections and with mild-moderate symptoms, a course with a csDMARDs at full dose may be tried (strength of recommendation C).

Choice of drug

As there are no studies comparing the efficacy of the various bDMARDs and APR on active enthesitis in patients with PsA, these drugs may all be used as first line agents in the treatment of this clinical feature (strength of recommendation A). Likewise the other articular manifestations of this disease, the choice of the drug should be driven by other concomitant articular features, extra-articular manifestations, global health status, patient's preference, safety data, physician's confidence with the drugs, and costs. For the sake of cost-reduction, when IFX and ETA are chosen, the licensed biosimilar products rather than the originators could be used.

Monitoring of disease activity and therapy response

The first evaluation should be carried out after three months of therapy. Patient's evaluation of pain (10-cm VAS), and/or global disease activity (10-cm VAS), and/or disability (HAQ-DI) should be primarily used to assess enthesitis activity and monitor therapy response. An objective examination of the enthesial involvement is also advisable. Among the various existing indices for the measurement of enthesitis, the LEI is the only one specifically developed and validated for PsA (96). However, for clinical practice, we suggest to assess presence of tenderness in the following enthesial sites: lat-

eral epicondyles, greater trochanters, quadriceps tendons, proximal and distal insertion of the patellar tendons, Achilles tendon insertions, and plantar fascia insertions. As PDUS was proven to be more sensitive in detecting enthesitis, when available this imaging method may be associated to clinical examination in the assessment of this disease manifestation. In this case, one among the many scoring systems proposed for enthesitis should be used (97).

Patients are considered responder to the therapy if the following two conditions are satisfied:

3. Achievement of remission (absence of enthesitis) or, if not feasible, low disease activity, defined by patient pain on VAS ≤ 15 and/or patient global activity on VAS ≤ 20 and/or HAQ-DI ≤ 0.5 , or by fulfilling the MDA criteria. If available, PDUS may be used.
4. Expert's opinion that a good response has been achieved and, therefore, that the therapy should be continued.

We suggest the same times and modalities of response assessment as those indicated for peripheral joint arthritis.

Management of patients who fail a bDMARD or APR

There are no data to indicate the best strategy to treat PsA enthesitis non-responder to a first bDMARD or APR. On the basis of our judgement we suggest the following (strength of recommendation C):

- A. TNFi failure due to primary lack of efficacy: swapping to another MOA or switching to another TNFi.
- B. TNFi failure due to secondary loss of efficacy: switching to another TNFi.
- C. TNFi failure due to adverse event: if the adverse reaction is likely to be a class effect, swapping to another MOA, otherwise switching to another TNFi.
- D. bDMARDs other than TNFis and APR failure: there is no alternative to swapping to another MOA.

Once again, the choice of the therapy should also be based on the global clinical picture of the patient (development or worsening of extra-articular manifestations, other comorbidities).

How to manage disease remission

No formal study has ever evaluated the management of PsA enthesitis once remission has been achieved with bDMARDs or APR. A few cases have been reported of successful withdrawal of TNFi after enthesitis resolution in patients with B27⁺ peripheral SpA (98, 99). In these cases enthesitis had reoccurred after a long period without therapy and it had subsided completely with retreatment. In our opinion, in the case of enthesitis in complete remission for at least six months the therapy may be first tapered to half of the starting dose and then discontinued after six months (strength of recommendation C). In the case of partial remission our advice is to reduce the therapy to half of the initial dose (strength of recommendation C). Patients should be informed about risks and benefits of treatment reduction or withdrawal, and they should be actively involved in this decision. Patients that after therapy modification show signs of enthesitis relapse should immediately go back to the full dose of the previous drug.

Dactylitis

TNFis

The topic of the efficacy of the TNFis on psoriatic dactylitis was specifically addressed in the respective RCTs only for IFX, GOL, and CZP (18, 19, 28, 32). All of these drugs proved to be superior to placebo in improving dactylitis (level of evidence Ib). Likewise enthesitis, in the ADEPT study, ADA was non-significantly better than placebo in controlling dactylitis, but data were not presented (explorative endpoint) (25). However, ETA and ADA were shown to improve dactylitis in two observational studies (17, 95) with no control group (level of evidence 3). In all of the above mentioned studies, dactylitis outcome measures were rather heterogeneous, varying from number of involved digits (with or without 0-3 severity scales), to percentage of patients with dactylitis, and to the use of the Leeds Dactylitis Index. This makes even indirect comparisons between the various molecules not possible. Overall, on the basis of evidence and clinical experience, it is generally

reckoned that TNFi are effective on PsA dactylitis as a class, regardless of the lack of proper data on the topic for two of them.

IL23i, IL-17i, and PDE4i

A post-hoc analysis made by pooling the data of PSUMMIT1 and 2, showed that UST therapy at week 24 had induced a reduction in the number of patients with dactylitis significantly higher than placebo (the percentage of the patients with dactylitis was 51.8% in the UST groups and 75.6% in the placebo groups, vs. baseline) (level of evidence Ib) (100).

In the FUTURE 1 trial, at week 24 resolution of dactylitis occurred in 52.4% of the SEC-treated patients vs. 15.5% of the placebo treated patients (significant difference) (level of evidence Ib) (40). In the FUTURE 2 trial, the percentage were 47% for SEC (150 and 300 mg pooled data) and 15% for placebo, but this difference was not significant due to not achievement of a precedent target in the hierarchy scale (41).

In the PALACE 1 trial, at week 24, a dactylitis score of 0 was achieved by 50.9% and 47.7% of the patients in the APR group (20 and 30 mg, respectively) and 40.9% of those in the placebo group (difference not significant) (46). In the PALACE 3 trial, at week 24, mean change in dactylitis score was significantly improved for APR 30 mg (-2.4) vs. placebo, but not for APR 20 mg (level of evidence Ib) (51).

Overall, these studies indicate that UST, SEC, and APR at 30 mg are effective in the treatment of PsA dactylitis.

Inclusion criteria

Therapy with bDMARDs or APR should be considered for PsA dactylitis if:

1. At least one digit presents acute dactylitis. A digit is considered acutely inflamed if it is swollen, painful and tender and other possible causes are reasonably excluded. A digit is defined swollen if the soft tissues from the metacarpophalangeal joint to the digital tuft are swollen to the extent that the actual joint swelling could no longer be independently recognised and its circumference at

level of the first phalanx is at least 10% greater than the contralateral. If available, PDUS may be used to confirm the diagnosis of acute dactylitis.

2. Treatment with local GC injections and NSAIDs have proven ineffective (strength of recommendation C).
3. According to the expert's opinion a therapy is indicated. This opinion should be mainly based on patient's evaluation of quality of life and/or pain. Instruments suitable for this evaluation, such as HAQ-DI, 10-cm VAS for pain, and 10-cm VAS for global disease activity, may be used. Objective signs of joint damage may also be considered.

In patients with mild-moderate dactylitis, a course with a csDMARDs at full dose may be tried (strength of recommendation C).

Choice of drug

Given the lack of studies comparing the efficacy of the various bDMARDs and APR on PsA dactylitis not responsive to the first line of therapy, each of these drugs may be used as first line agent for the treatment of this clinical manifestation (strength of recommendation A). Similarly to the other articular manifestations of PsA, the choice of the drug should be based on other concomitant articular features, extra-articular manifestations, global health status, patient's preference, safety data, physician's confidence with the drugs, and costs. As biosimilar IFX and ETA are cheaper than their originators, they could be the first choice when these molecules are indicated.

Monitoring of disease activity

The first evaluation should be performed after three months of therapy. For the assessment of dactylitis we suggest counting the number of digits with acute dactylitis and scoring the degree of tenderness of each involved digit on a 0–3 scale. Subjective evaluations should always be used for monitoring disease activity, regardless of the clinical manifestation. For dactylitis we suggest the evaluation of pain on a 10-cm VAS. Other more comprehensive instruments, such as patient's evaluation

of global disease activity and HAQ-DI, may be used. When available, also PDUS may be used for the assessment of dactylitis. Patients are considered responder to the therapy if the following two conditions are satisfied:

1. Achievement of remission (absence of dactylitis) or, if not feasible, low disease activity, defined by patient pain on VAS ≤ 15 and/or patient global activity on VAS ≤ 20 and/or HAQ-DI ≤ 0.5 , or by fulfilling the MDA criteria. If available, PDUS may be used.
2. Expert's opinion that a good response has been achieved and, therefore, that the therapy should be continued.

We suggest the same times and modalities of response assessment as those indicated for peripheral joint arthritis and enthesitis.

Management of patients

who fail a bDMARD or APR

There are no data to indicate the best strategy to treat PsA dactylitis non-responder to a first bDMARD or APR. On the basis of our judgement we suggest the following (strength of recommendation C):

- A. TNFi failure due to primary lack of efficacy: swapping to another MOA or switching to another TNFi.
- B. TNFi failure due to secondary loss of efficacy: switching to another TNFi.
- C. TNFi failure due to adverse event: if the adverse reaction is likely to be a class effect, swapping to another MOA, otherwise switching to another TNFi.
- D. bDMARDs other than TNFis or APR failure: there is no alternative but swapping to another MOA.

Also for the choice of the second line of biologic therapy, the global clinical picture of the patient (other articular involvements, development or worsening of extra-articular manifestations, other comorbidities) should guide the decision.

How to manage disease remission

No study has ever addressed the management of PsA dactylitis once remission has been achieved with b-

DMARDs or APR. In our opinion, if dactylitis has been in remission for at least six months, the therapy may be first tapered to half of the starting dose and then discontinued after six months (strength of recommendation C). In the case of partial remission our advice is to reduce the therapy to half of the initial dose (strength of recommendation C). Patients should be informed about risks and benefits of treatment reduction or withdrawal, and they should be actively involved in this decision. Patients that after therapy modification show signs of dactylitis relapse should immediately go back to the full dose of the previous drug.

Spondylitis

Symptomatic axial involvement is a common feature of PsA, ranging from 20 to 40% of patients, and has an impact on functional capacity, global disease activity, and quality of life, comparable to that of AS (101). Nevertheless, treatments for axial PsA have not been specifically studied and, as a result, there are no data on this topic. In PsA trials, only small numbers of patients were classified as having predominant spondylitis, and, similarly, small numbers of patients in AS trials had psoriasis. An observational study of patients with axial PsA showed that, over a 12-month period, ETA therapy improved all of the usual indices of disease activity (102). The lack of specific studies in axial PsA patients has led to the adoption of treatments and outcome measures developed for AS, assuming that the two conditions (AS and axial PsA) are equivalent. This approach has been used for the systematic literature reviews (7, 10) informing GRAPPA and EULAR recommendations for the treatment of PsA.

TNFis

All of the five TNFis are highly effective in AS, decreasing disease activity and, consequently, improving quality of life (level of evidence Ia), both at short and long-term (103). The efficacy of these drugs has also been proven for non-radiographic axial SpA by several RCTs (level of evidence Ia) (103). It should be mentioned, however, that in

the ADA study psoriasis and PsA were exclusion criteria (104) and that in the other studies psoriasis subsets were not defined (105-108). Interestingly, in contrast to their good efficacy on the clinical manifestations of axial SpA, the ability of TNFis to inhibit radiographic progression remains to be established. (109, 110). No data whatsoever on this aspect is available for axial PsA.

IL-23i

In PSUMMIT 1, UST-treated patients showed a significant Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 20 and 70 (but not 50) response at the 45 mg dose and a significant BASDAI 20/50/70 at the 90 mg dose (36). This result, however, was related to the entire study population, and not to only the patients with axial involvement. Recently, a post-hoc analysis of PSUMMIT 1 and 2 studies focusing on the PsA patients with physician-reported spondylitis has been published (111). In this spondylitic subset (164 UST and 92 placebo), at week 24, significantly more UST than placebo-treated patients achieved a BASDAI 20/50/70 response (54.8%, 29.3% 15.3% vs. 32.9%, 11.4%, 0%; $p \leq 0.002$), an improvement in BASDAI question two concerning axial pain (1.85 vs. 0.24; $p < 0.001$), and an Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP improvement (27.8% vs. 3.9%; $p < 0.001$). Finally, in a proof-of-concept study in 20 patients with AS, at week 24 the primary endpoint was achieved by 65% of them, and all of other indices of disease activity showed a substantial improvement (level of evidence 3) (112).

IL-17i

Data on the effect of SEC in axial PsA are not available. Two pivotal phase-III RCTs (MEASURE 1 and-2) have evaluated the efficacy of this drug in patients with AS (113). In MEASURE 1, at week 16, the Assessment of SpondyloArthritis International Society (ASAS) 20 response rates was 61%, 60%, and 29% for SEC 150 mg, SEC 75 mg, and placebo, respectively ($p < 0.001$ for both doses vs. placebo); in MEASURE 2 the corresponding

figures were 61%, 41%, and 28% for SEC 150 mg, SEC 75 mg and placebo, respectively ($p < 0.001$ for the 150 mg dose and $p = 0.10$ for the 75 mg dose). In MEASURE 2, all of the secondary end points, except ASAS partial remission, were met with SEC 150 mg. Therefore, SEC is effective in AS (level of evidence Ib).

PDE4i

In the PALACE studies the effect of APR on axial disease has not been specifically addressed. In a pilot, phase II, placebo-controlled study, 38 patients with AS were randomised to APR 30 mg BID or placebo over a 12-week period (114). All of the clinical measures improved more with APR than with placebo, but the difference was not statistically significant. ASAS20 response was achieved by 35.3% of the APR-treated patients and 15.8% of the placebo-treated patients. More data on this topic are clearly needed.

Inclusion criteria

As already mentioned, the following recommendations are largely based upon the evidence provided by the studies on axial SpA and follow the international indications for the treatment of this condition (115, 116). The initial treatment should rest on NSAIDs, at least two of them for four weeks, each at full dose. As csDMARDs have not proven effective in this condition, they should not be used for the therapy of axial PsA. Due to the lack of evidence, also APR should not be used to treat psoriatic spondylitis.

Therapy with bDMARDs should be considered in patients with PsA predominantly characterised by axial involvement (sacroiliitis and/or spondylitis) if:

1. They have active disease (BASDAI ≥ 4).
2. They have not responded over a 4-week period to full doses of NSAID therapy (at least two of them).
3. They are suitable for a therapy with biologics according to the expert's opinion. This opinion should consider clinical features, serum acute phase reactant levels, and imaging findings.

Choice of drug

TNFis and SEC may be used as first line agents to treat active axial PsA resistant to NSAIDs (strength of recommendation A for axial SpA). UST has not been evaluated by specific trials and its use may be considered in case of contraindication to the other bDMARDs (strength of recommendation C). As already stated for the other articular manifestations of PD, the choice should be based upon the global clinical picture of the individual patient, patient's preference, safety data, physician's confidence with the drugs, and last, but not least, costs. When IFX or ETA are indicated, the licensed biosimilar products, rather than the originators, could be used.

Monitoring of disease activity

Likewise the other manifestations of PsA, also for the axial involvement remission should be the target of the therapy. Biologically, this state may be defined as a complete disappearance of signs and symptoms (*i.e.*, pain, stiffness, and restriction in spinal mobility), return to a normal physical function and quality of life, and inhibition of progression of structural damage. If remission is not achievable, a state of residual low disease activity may be considered acceptable. Remission and minimal disease activity are possible targets when treating PsA patients with axial involvement (117). The first assessment should be performed after three months of therapy. Although outcome measures specific for axial PsA are still under active investigation, the instruments for AS have been shown to perform well when applied to PsA (118). Among these tools, we recommend the BASDAI, for a subjective evaluation, and the Bath Ankylosing Spondylitis Metric Index (BASMI), for an objective assessment. We also suggest to monitor the CRP serum levels. If not employed for the other articular manifestations of the same patient, pain on 10-cm VAS, patient's global disease activity on 10-cm VAS, and HAQ-DI should also be collected. If a measurement of radiographic progression is required, we recommend the PASRI (Psoriatic Arthritis Spondylitis

Radiologic Index) (119) more than the BASRI (Bath AS Radiology Index) or the m-SASSS (modified Stoke AS Spine Score) (120).

Patients are considered responder to the therapy if the following two conditions are satisfied:

1. Achievement of remission (by clinical judgement) or at least $\geq 50\%$ relative or \geq two-point absolute improvement in the BASDAI score plus normal CRP serum levels.
2. Expert's opinion that a good response has been achieved and, therefore, that the therapy should be continued.

We suggest the same times and modalities of response assessment as those indicated for peripheral joint arthritis, enthesitis, and dactylitis.

Management of patients

who fail a bDMARD

CZP pivotal trial on axial SpA (RAPID-axSpA) is the only study with TNFis where a group of patients (about 15%) had previously failed a TNFi (because of secondary loss of efficacy or AEs), but separate data for this group have not been reported (106). Data on TNFi switching in AS basically come from observational cohorts (level of evidence 3). In the DANBIO registry, nearly one-third of the 1,436 AS patients starting TNFi treatment switched to another TNFi (121). Even if response rates and drug survivals were lower among switchers, half of them showed treatment response. Similar results have been reported by other studies (122, 123). In the MEASURE 2 study, more than one-third of the patients treated with SEC had been IRs to a previous TNFi. At week 16, the primary endpoint (ASAS20 response) was achieved by 68.2% of the TNFi-naïve patients and 50% of the TNFi-IR patients (for both doses the response rate was significantly better than for placebo) (level of evidence Ia) (124). There are no studies on switching or swapping bDMARDs in axial PsA and no data about swapping from TNFi to SEC in axial SpA.

On the basis of these data and our judgement, in the case of bDMARD failure we advise the following strategies (strength of recommendation B for AS):

A. TNFi failure due to primary lack of efficacy: swapping to SEC or switching to another TNFi.

B. TNFi failure due to secondary loss of efficacy: switching to another TNFi.

C. TNFi failure due to adverse event: if the adverse reaction is likely to be a class effect, swapping to SEC, otherwise switching to another TNFi.

D. SEC failure: there is no alternative to swapping to a TNFi.

If TNFis and SEC are ineffective or contraindicated, UST may be tried.

As already suggested for the other articular manifestations, the global clinical picture of the patient should be taken into account when deciding the next therapy.

How to manage disease remission

Once again, due to the total lack of data on the outcome after treatment tapering or withdrawal of patients with axial PsA who have entered remission with TNFis, axial SpA is used as reference. The available data indicate that the great majority of patients with AS in remission flares after withdrawal of TNFi therapy (125-127). In contrast, there is evidence showing that tapering of TNFi in AS patient in sustained remission is successful in most cases (128-130). No study on drug withdrawal or dose reduction in patients with axial SpA treated with SEC or UST has ever been conducted.

In our opinion, patients with axial PsA in clinical remission for at least six months are possible candidate for cautious dose reduction, if in the expert's opinion this is feasible (strength of recommendation B). In contrast, in these patients therapy withdrawal is not advisable (strength of recommendation B).

Extra-articular manifestations

Due to the heterogeneous presentation of PD, the treatment should be individualised according to both articular and extra-articular manifestations, such as psoriasis, uveitis, Crohn's disease (CD) or ulcerative colitis (UC). All of the antibody TNFis showed their efficacy in the treatment of psoriasis and CD and in reducing the number of recurrences of uveitis (131, 132) (level of evidence

Ib). IFX, ADA, and GOL also proved to improve CU (6) (level of evidence Ib). Although direct comparison trials are lacking, ETN seems to be less efficacious on psoriatic skin lesions than other TNFis and it showed contradictory results in uveitis (133) and no efficacy in inflammatory bowel disease (IBD) (134, 135). Currently, in Italy IFX and ADA may be used in psoriasis and IBDs; GOL in psoriasis but not yet in IBDs, although it showed efficacy in UC (136); ETA in psoriasis only; CZP, although efficacious (137, 138), in none of these conditions because still not registered.

Patients with moderate or severe psoriasis seem to respond better to IL12/IL23 or IL17 inhibitors than TNFis (level of evidence Ia). A meta-analysis found that in the treatment of plaque psoriasis, UST is more efficacious than ADA and ETA (139). Direct comparison trials in psoriatic patients showed a greater efficacy of SEC when compared to ETA (140) and UST (141). UST was proven efficacious in active Crohn's disease (142) (level of evidence Ib) and it has been recently approved in Europe for the treatment of this condition. SEC does not seem to be associated with an increased risk of IBD (68) but it is not indicated to treat patients with this disorder, as clearly stated by the SCPs of this drug. Finally, SEC proved its efficacy in the treatment of non-infectious uveitis (143) (but no data on PsA-related uveitis are currently available) and studies on the efficacy of UST in uveitis have not been published. APR is efficacious in psoriasis (144) (level of evidence Ib) but not yet registered in Italy for this indication. There are no data on the use of APR in patients with IBD or uveitis.

Choice of drug

In PsA patients with severe skin involvement, all of licensed bDMARDs may be used but taking into account that ETA is less effective than the other TNFi and that UST and SEC induce a greater psoriasis improvement than TNFis. PsA patients with uveitis requiring a systemic treatment with bDMARDs should be treated with TNFis, preferably with a monoclonal antibody.

Finally, in our opinion, in PsA patients with concomitant IBD requiring a systemic treatment with bDMARDs, the monoclonal TNFis and UST are the most appropriate choices. In PD patients in whom treatment with bDMARDs should be started because of manifestations other than arthritis we recommend the therapy be driven by the appropriate specialist at the doses indicated for that specific condition.

Discussion

Herein, the SIR "Spondyloarthritis and Psoriatic Arthritis study group – A. Spadaro" presents an update of the SIR recommendations for the use of bDMARDs and other novel agents in PsA. This new version of the recommendations is different from the old ones in many respects. As in the fast-changing world of the treatment of the inflammatory arthritides molecules different in structure and mechanisms of action from the so-called biologics are continuously being developed, all of the new drugs tested in PsA have been dealt with, encompassing the new tsDMARDs. Although, some of the agents discussed herein are not registered for the treatment of PsA in Italy, they have been included either because they are very likely to be licensed in a relatively short time or because rheumatologists are very familiar with them due to their use in RA. For all of the bDMARDs and for the new tsDMARDs the most relevant evidence are presented, in deeper detail for the drugs that had not been dealt with in the previous recommendations.

Other relevant differences with the past versions of the recommendations are in the inclusion criteria. In this edition, we do not suggest specific threshold values for the various indices of disease activity because, in our opinion, a flexibility in the inclusion criteria will make them more applicable in daily clinical practice. However, we strongly recommend that, in PsA, bDMARDs and tsDMARDs be used only by rheumatologists expert in this condition and that the prescription of these drugs be restricted to qualified centres. We also emphasise that main instruments for the assessment of disease activity, quality of life, and damage accrual should

be constantly used to evaluate therapy indication and response. In addition, differently from the past versions of the recommendations, a section on the effects of the various drugs on the main extra-articular manifestations of the PD has been added.

The conceptual framework of the previous recommendations has been maintained. The different clinical articular manifestations of PsA have been separated and for each of them inclusion criteria, suggestion for therapy choice, indication for the assessment of that specific domain, criteria of therapy response and suggestions for therapy modifications in case of failure or remission have been provided. However, we would like to emphasise that as most of the patients with PsA show a mixture of the various manifestations of PD, the choice of the therapy should be tailored on the individual patient taking into account his/her global clinical picture.

The recently published EULAR (5) and GRAPPA (6) recommendations for the treatment of PsA have used different approaches for choice of the therapy. In the former, a hierarchy of the various drugs is suggested, with TNFis usually indicated as first line. In the latter, the indications are purely evidence-based, and all of the drugs with proven efficacy for that specific clinical domain are recommended without preferences. In our opinion, given the multiplicity of the factors that influence the therapy decision (including patient's preference, comorbidities, and cost of the drug), it is more convenient to have the possibility of selecting, among several agents, the more indicated for each individual patient. Our indications on the various aspects of the treatment of PsA have been guided by the available evidence. Some domains, however, are not fully covered by solid evidence and for them we have provided suggestions based on indirect evidence or experts' opinion. Combination therapy with MTX or other sDMARDs, utility of a treat-to-target approach, switching or swapping in case of primary or secondary therapy lack of efficacy, strategy for patients with a good response on symptoms but progression of radiographic damage, drug choice based on biomarkers pre-

dictive of optimal response, and management of disease remission are some of the issues needing a better definition and belong to the current and future research agendas.

Given the continuous acquisitions in all of the domains of PsA and the large number of new drugs for this disease presently under development, these recommendations will require further updating in a few years.

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