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Management of Peripheral Arthritis in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

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ABSTRACT. ***Objective.*** We aimed to compile evidence for the efficacy and safety of therapeutic options for the peripheral arthritis domain of psoriatic arthritis (PsA) for the revised 2021 Group in Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations.

Methods. A working group consisting of clinicians and patient research partners was convened. We reviewed the evidence from new randomized controlled trials (RCTs) for PsA treatment from February 19, 2013, to August 28, 2020. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-informed approach to derive evidence for the classes of therapeutic options for 3 patient groups: (1) naïve to treatment, (2) inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and (3) inadequate response to biologic DMARDs (bDMARDs). Recommendations were derived through consensus meetings.

Results. The evidence review included 69 RCTs. We derived GRADE evidence for each class of therapeutic options and achieved consensus for the recommendations. For patients naïve to treatment, the working group strongly recommends csDMARDs (methotrexate, sulfasalazine, leflunomide) and phosphodiesterase 4 inhibitors, and emphasizes regular assessment and early escalation to achieve treatment target. bDMARDs (tumor necrosis factor inhibitors [TNFi], interleukin 17 inhibitors [IL-17i], IL-12/23i, IL-23i) and Janus kinase inhibitors (JAKi) are also strongly recommended. For patients with inadequate response to csDMARDs, we strongly recommend TNFi, IL-17i, IL-12/23i, IL-23i, and JAKi. For those who had prior experience with bDMARDs, we strongly recommend a second TNFi, IL-17i, IL-23i, and JAKi. The evidence supporting nonpharmacological interventions was very low. An expert panel conditionally recommends adequate physical activity, smoking cessation, and diet to control weight gain.

Conclusion. Evidence supporting optimal therapy for the peripheral arthritis domain of PsA was compiled for the revised 2021 GRAPPA treatment recommendations.

Key Indexing Terms: GRAPPA, peripheral arthritis, practice guideline, psoriatic arthritis, psoriasis, systemic literature review

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Psoriatic arthritis (PsA) is a complex systemic disease involving peripheral arthritis, axial involvement, dactylitis, enthesitis, and skin and nail psoriasis.[1] Peripheral arthritis is one of the cardinal features of PsA, and the majority of patients with PsA may have oligoarthritis or polyarthritis at some point in their disease course.[2] Peripheral arthritis tends to progress over time; 47% of patients had developed radiographic erosion at 2 years,[2] and over a half of patients had more than 5 damaged joints at 5 years.[3] Peripheral arthritis is one of the key domains in PsA and the most carefully studied in relation to treatment response. It is included in the previous 2 recommendation guidelines by the Group in Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).[4,5] To support the development of updated treatment recommendations for PsA, we aimed to update the evidence for interventions for peripheral arthritis in PsA.

METHODS

A working group for peripheral arthritis was convened under GRAPPA, with 30 members from 20 countries in 5 continents (Africa, Asia, North America, South America, and Europe) led by 2 group leaders (YYL and OF). The group consisted of 28 rheumatologists and 2 patient research partners (PRPs; RF and WO).

Engagement of perspectives of patient. The 2 PRPs participated in all stages of the research process, including formulating review questions, selecting critical outcomes, synthesizing evidence, proposing recommendations, and phrasing agreement statements for Delphi exercises. Four PRP engagement webinars were conducted throughout the process to ensure the background, methodology of the project, and Delphi exercises were understood.

Review question formulation. The working group formulated the following 6 research questions according to PICO (Patient/Population – Intervention – Comparison/Comparator – Outcome)[6] to address the effect of any pharmacological and nonpharmacological treatments for patients with PsA who have active peripheral arthritis with different characteristics:

1. In patients who are treatment naïve, what is the effect of the available treatments compared to placebo?
2. In patients who are treatment naïve, what is the effect of biologic disease-modifying antirheumatic drugs (bDMARDs) compared to conventional synthetic DMARDs (csDMARDs)?
3. In patients who have inadequate response to csDMARDs, what is the effect of the available treatments compared to standard of care?
4. In patients who have inadequate response to csDMARDs, what is the effect of the available treatments compared to tumor necrosis factor inhibitors (TNFi)?
5. In patients who have inadequate response to bDMARDs, what is the effect of available treatments compared to standard of care?
6. In patients with active peripheral arthritis, what is the effect of nonpharmacological treatments compared to standard of care?

Literature search. The methods of this evidence review have been outlined previously.[7] Methodologists (NC, DvdW) with experience in searches and evidence synthesis were engaged. Searches were undertaken using MEDLINE, EMBASE, and the Cochrane library from February 19, 2013, to August 28, 2020. Search terms are listed in the previous publication.[8]

Data extraction and risk of bias assessment. Thirteen researchers from GRAPPA extracted the data onto a standardized Excel spreadsheet. The quality assessment of each article was read by a GRAPPA researcher and 1 methodologist. Effect sizes for the main outcomes in each article were summarized using a color-coding system developed for this project (Supplementary Material 1, available with the online version of this article). In brief, green represents superiority to comparator, amber represents no statistically significant difference to comparator, red represents inferiority to comparator, and blue represents data not reported.

Selection of critical outcomes for peripheral arthritis in PsA. The working group members participated in a webinar discussion and Delphi exercises to reach consensus on the critical outcomes for the assessment of therapies. We summarized the body of evidence to support each class of treatment and graded the certainty of the evidence using an approach informed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[9-11] Six working teams were convened for the 6 PICO questions for the body of evidence supporting the following classes of treatment: csDMARDs, phosphodiesterase type 4 inhibitor (PDE4i),

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TNFi, interleukin 17 inhibitor (IL-17i), IL-12/23i, IL-23i, Janus kinase inhibitors (JAKi), dual IL-17/TNFi, cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion proteins (CTLA4-Ig), and IL-6i. Each team comprised a team leader (SJP, YYL, LC, or TVK) and 4 to 8 members to appraise the body of evidence for each critical outcome in supporting each class of treatment. The evidence supporting the previous GRAPPA recommendations[4,5,12] was also reviewed. When no new data were found for a class of treatment, the working group adopted the previous recommendations.[5] The GRADE-informed approach represented the certainty of the evidence considering the study design, risk of bias of studies, consistency of results across studies, indirectness of evidence, imprecision, publication bias, magnitude of effect sizes, dose-dependent response, and residual confounders. Using the GRADE-informed approach, the evidence was rated as high ⨁⨁⨁⨁, moderate ⨁⨁⨁⊖, low ⨁⨁⊖⊖, or very low ⨁⊖⊖⊖.[10]

We followed the GRADE methodology to draw conclusions regarding the strength of the proposed recommendations into 4 categories: strongly recommend, conditionally recommend, conditionally against, and strongly against.[9,11] High-quality evidence does not necessarily imply strong recommendations, and strong recommendations can arise from low-quality evidence. The balance between the quality of evidence, desirable and undesirable effects, variability in values and preferences, and resources use were considered.[9,11] In areas where certainty in the evidence was low or very low, special working teams were formed to propose recommendations. The proposed recommendations from each PICO team were discussed to reach consensus among all the working group members. Further modulations with the entire GRAPPA recommendation development group were conducted.

Consensus building. All GRADE evidence and recommendations derived for each PICO question were summarized in tables. All 30 members in the peripheral arthritis working group were invited to participate in anonymized Delphi exercises on the proposed recommendations. For each recommendation, members were asked to indicate their agreement on an 11-point numeric rating scale (0 = no, do not agree at all, to 10 = totally agree). It was prespecified that a score of 7 out of 10 generally indicates agreement.[3] An achievement of consensus is considered when 70% of the members voted an agreement score of 7 out of 10.[3] Up to 3 rounds of discussion and Delphi exercises were conducted to achieve consensus.

RESULTS

Seventy studies (including 15 unpublished abstracts) were included from the literature search (Figure 1). Six studies were excluded because of mixed population or no peripheral arthritis outcomes by consensus of the peripheral arthritis working group. One conference abstract published after the search date was reviewed as a full paper.[13] As there were no new studies identified for csDMARDs, we reviewed 5 studies from the previous systematic review.[12] The final number of studies included was 69. The study design and baseline characteristics of patients with PsA for all included studies are summarized in Supplementary Material 2 (available with the online version of this article).

Selection of critical outcomes for peripheral arthritis in PsA. Group members participated in 3 Delphi exercises and 1 webinar discussion. From the 40 possible outcomes related to peripheral arthritis, consensus was reached on 14 critical outcomes: American College of Rheumatology (ACR) 20/50/70, Disease Activity Score in 28 joints (DAS28), minimal disease activity (MDA), patient global assessment (PtGA), Disease Activity Index for Psoriatic Arthritis (DAPSA), 66-joint swollen joint count and 68-joint tender joint count (SJC66 and TJC68, respectively), pain, Health Assessment Questionnaire–Disability Index (HAQ-DI), 36-item Short Form Health Survey physical component summary (SF-36 PCS), van der Heijde modified total Sharp score (mTSS), and adverse events Supplementary Material 3 (available with the online version of this article). These critical outcomes encompass disease activity in peripheral joints, the impact of PsA, structural damage, and adverse events. The results of the Delphi exercises and discussion points are shown in Supplementary Material 3.

Risk of bias assessment and effect size appraisal. The risk of bias assessment and the effect sizes appraisal of peripheral arthritis outcomes for each class of therapies are summarized in Supplementary Material 4 (available with the online version of this article).

Evidence synthesis. Evidence supporting optimal treatment were derived for 3 groups of patients: (1) treatment naïve, (2) inadequate response to csDMARDs, and (3) inadequate response to bDMARD. The GRADE evidence derived for each class of treatment and each critical outcome are summarized in Table 1 to Table 4. The details of all GRADE tables for each class of treatment are shown in Supplementary Material 5 (available with the online version of this article). There were no new data found for nonsteroidal antiinflammatory drugs and intraarticular corticosteroids. The working group agreed on conditionally recommending them as per the 2016 GRAPPA treatment recommendations.[5,14] The finalized recommendations for the treatment of peripheral arthritis domain for patients with PsA are summarized in Figure 2.

Recommendations for treatment-naïve patients. There is low-to-moderate level of certainty in the evidence to support csDMARDs (methotrexate [MTX], sulfasalazine [SSZ], leflunomide [LEF]) being superior to placebo from randomized controlled trials (RCTs; Table 1). The working group also reviewed the clinical responses in the MTX monotherapy arm in 4 RCTs,[15-18] revealing reasonable clinical improvement with ACR20 responses ranging from 41% to 63%, and MDA ranging from 22% to 43%. In addition to these supportive observational data, csDMARDs have a long history of usage, are low cost, and are universally accessible. Opinion was divided on strongly vs conditionally recommending csDMARDs in treatment-naïve patients. In the first and second Delphi exercises (response rates 93% and 90%, respectively), only 56% voted for strongly recommending csDMARDs. In the third Delphi exercise (response rate 93%), the working group discussed and balanced the low level of evidence to support csDMARD use from RCTs, with supportive observational data, long experience of usage, low cost, and universal access. We therefore strongly recommended csDMARDs (MTX, SSZ, LEF). In most circumstances, csDMARDs can be initiated as first-line therapy and assessed regularly for response and possible escalation of therapy. Aligning with the previous GRAPPA recommendations,[5] the working group recommended considering early escalation of therapy, particularly for those with poor prognostic factors (eg, increased levels of inflammatory markers, high active joint counts). Agreement votes (7/10)[3] were achieved in 92.9% of working group members (Table 1).

Added to a previous open-label RCT,[19] a high level of

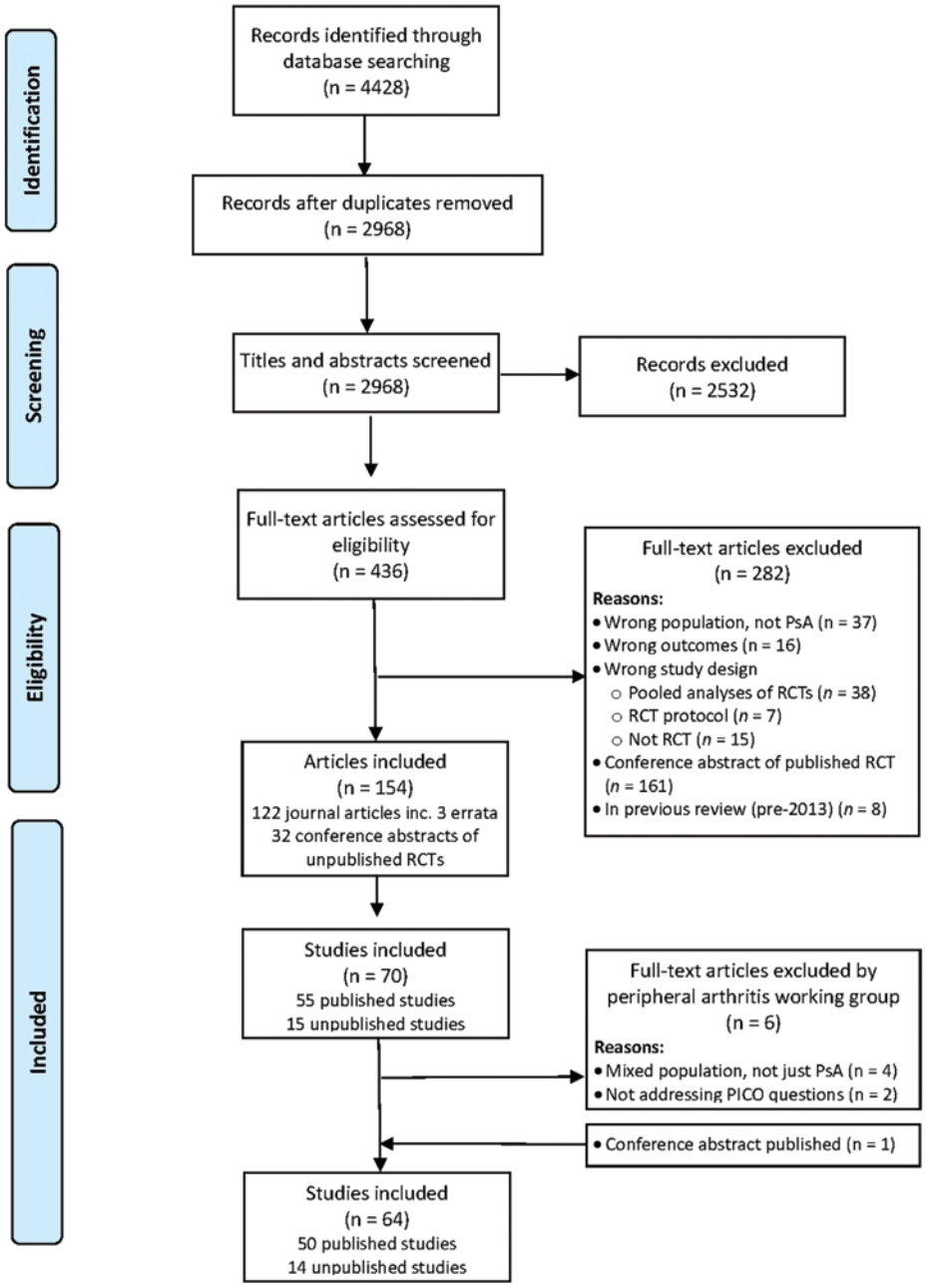

Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PsA: psoriatic arthritis; RCT: randomized controlled trial.

evidence from double-blind RCTs has emerged for treatment-naïve patients with PsA, demonstrating superiority of TNFi in clinical responses, disease impact,[16-18] and lower radiographic progression[17] compared to placebo. In a large RCT involving 851 patients randomized to receive MTX, etanercept (ETN), or the combination, ACR20 was significantly higher in the ETN or combination arm compared to MTX (60.9% and 65.0% vs 50.7% at week 24, respectively). Significantly lower disease impact and less radiographic progression were seen in the ETN or combination arm compared to the MTX arm at week 48.[17] Similar superiority of TNFi compared to MTX in various peripheral joint outcomes was seen in 2 smaller RCTs, in which csDMARD-naïve patients were treated with MTX alone or in combination with golimumab.[16,18] Remarkably, in 1 RCT of patients with early PsA (mean disease duration 0.5 yrs), the DAS28 remission and MDA rates for patients in the TNFi/MTX combination arm were double compared to those in the MTX alone arm.[16] In summary, for DMARD-naïve patients, there is a high level of evidence to support TNFi being superior to MTX. Yet, the working group also considered the reduced accessibility of bDMARDs compared to csDMARDs, and the lack of evidence on whether a short delay in bDMARD

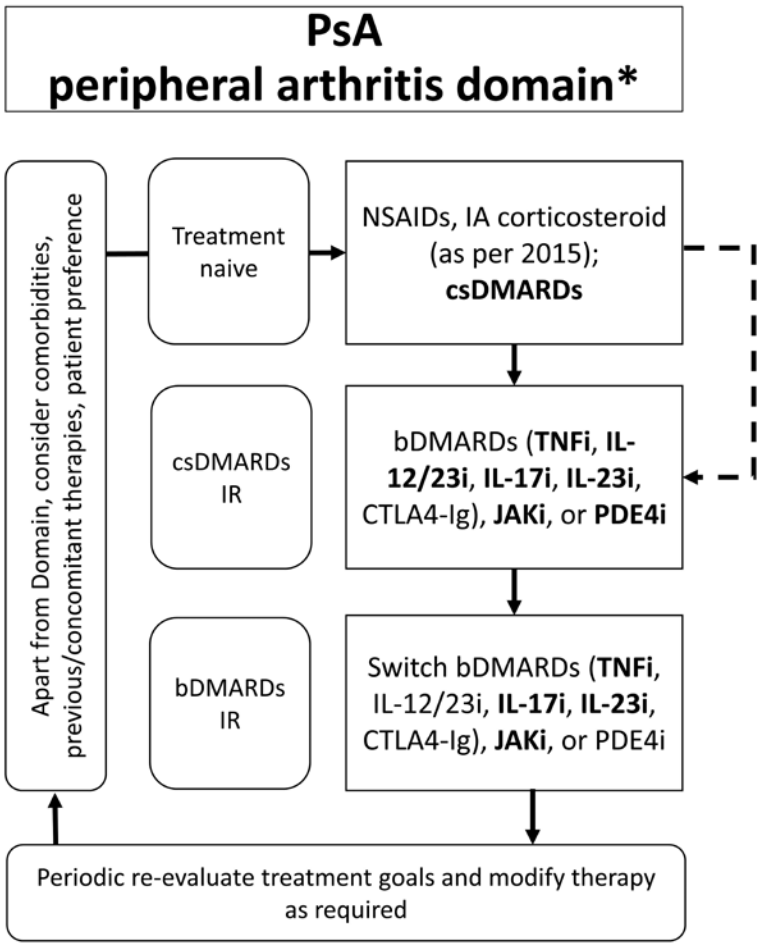

Figure 2. Schematic diagram for treatment of peripheral arthritis of PsA. * Recommendations for other domains are reported separately by the respective working groups. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CTLA4-Ig: cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein; IA: intraarticular; IL-12/23i: interleukin 12/23 inhibitor; IL-17i: interleukin 17 inhibitor; IL-23i: interleukin 23 inhibitor; IR: inadequate response; JAKi: Janus kinase inhibitor; NSAID: nonsteroidal antiinflammatory drug; PDE4: phosphodiesterase type 4; PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitor.

initiation would detrimentally affect long-term outcomes. Therefore, the working group strongly recommended TNFi as first-line therapy based on physicians' assessment of disease severity and shared decision making with patients. Agreement votes were achieved in 78.6% of working group members (Table 1). As there was a moderate-to-high level of evidence to support PDE4i, TNFi, IL-17i, IL-12/23i, IL-23i, and JAKi being superior to placebo, the working group strongly recommended them, with agreement votes ranging from 82.1% to 89.3% (Table 1). In the subgroup analyses of RCTs, the efficacies of these classes of treatment for improving peripheral arthritis outcomes in PsA were similar among patients with or without combinations of csDMARDs. A combination of csDMARDs with these therapeutic agents is not necessary to achieve short-term response.

Recommendations for patients with inadequate response to csDMARDs. For patients with inadequate response to csDMARDs, there is a high level of evidence to support the use of TNFi, IL-17i, IL-23i, and JAKi, and a moderate-to-high level of evidence to support IL-12/23i being superior to continuing usual care (Table 2). The working group strongly recommended all these treatments (agreement 100%, achieved in the first Delphi exercise). As there is a moderate-to-high level of evidence to support PDE4i being superior to continuing usual care, the working group conditionally recommended PDE4i (agreement 70.4%, achieved in the second Delphi exercise).

Table 1. Class of pharmacological treatments compared to placebo in patients naïve to DMARDs.

Intervention	GRADE Evidence (Effect Size)															Recommendation	Consensus	
	MDA	PASDAS	ACR20	ACR50	ACR70	DAS28	DAPSA	SJC66/ TJC68	PtGA	Pain	HAQ-DI	SF-36 PCS	mTSS	AEs	Overall Evidence		Agreement Median (IQR)	Agreement ≥ 7/10 (%)
MTX	NA	NA	Moderate (ns)	NA	NA	Moderate (ns)	NA	Low (ns)	Moderate (sup)	Moderate (ns)	Moderate (ns)	NA	NA	Low (ns)	**Moderate** (ns)			
SSZ	NA	NA	NA	NA	NA	NA	NA	Low (ns)	Low (ns)	NA	NA	NA	NA	Very Low (ns)	**Low** (ns)	**Strong for**	9.0 (7.0-10.0)	92.9
LEF	NA	NA	Moderate (sup)	NA	NA	NA	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	NA	Low (ns)	**Moderate** (sup)			
LEF vs MTX	NA	NA	Very Low (ns)	Very Low (ns)	Very Low (sup)	NA	Very Low (ns)	Very Low (ns)	Very Low (ns)	Very Low (ns)	Very Low (ns)	NA	NA	Very Low (ns)	**Very Low** (sup)	**Not recommending preference LEF over MTX**		
PDE4i	NA	NA	High (sup)	Moderate (sup)	Moderate (sup)	High (sup)	NA	High (sup)	High (sup)	High (sup)	Moderate (sup)	High (sup)	NA	Low (ns)	**Moderate to high** (sup)	**Strong for**	7.5 (6.0-8.0)	73.0
TNFi	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	NA	High (sup)	NA	High (sup)	High (sup)	High (sup)	Moderate (sup)	Low (ns)	**High** (sup)	**Strong for**	9.5 (9.0-10.0)	89.3
TNFi vs MTX	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	High (sup)	Moderate (sup)	Moderate (sup)	Low (ns)	**High** (sup)	**Strong for TNFi as first line** [a]	8.5 (7.0-9.8)	78.6
IL-17i	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Low (ns)	**High** (sup)	**Strong for**	9.0 (8.0-10.0)	85.7
IL-12/23i	NA	NA	High (sup)	High (sup)	Moderate (sup)	High (sup)	NA	NA	NA	NA	High (sup)	High (sup)	Low (ns)	Low (ns)	**Moderate to high** (sup)	**Strong for**	8.5 (7.0-10.0)	82.1
IL-23i	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	High (sup)	High (sup)	NA	Low (ns)	**High** (sup)	**Strong for**	9.0 (7.3-10.0)	85.7
JAKi	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Moderate (sup)	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Low (ns)	**High** (sup)	**Strong for**	8.5 (7.0-9.0)	82.1
CTLA4-Ig	Very Low (ns)	Very Low (ns)	Very Low (sup)	Very Low (sup)	Very Low (ns)	Very Low (sup)	Very Low (sup)	NA	NA	NA	Very Low (sup)	Very Low (ns)	NA	Low (ns)	**Very Low** (sup)	**Conditional against**	8.5 (7.0-10.0)	96.4
Dual TNFi/ IL-17i	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	NA	NA	NA	Moderate (sup)	NA	NA	Very Low (ns)	**Moderate** (sup)	**Not making recommendation** [b,c]	9.0 (9.0-10.0)	96.4
IL-6i	NA	Very Low (NT)	Low (sup)	Very Low (NT)	Very Low (NT)	Very Low (NT)	NA	Very Low (NT)	NA	Very Low (NT)	Very Low (NT)	Very Low (NT)	NA	Very Low (ns)	**Low** (sup)	**Conditional against** [b]	10 (8.3-10.0)	89.3

Color coding for effect sizes: light green (sup): significantly superior to placebo or active comparator; light amber (ns): no significant difference to placebo or active comparator; blue (NT): data reported only graphically, or no statistical test reported. [a] For patients with poor prognostic factors, or for consideration of early escalation. [b] Not approved by authorities. [c] Not available in the market. ACR20/50/70: American College of Rheumatology 20/50/70 response criteria; AE: adverse event; CTLA4-Ig: cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease Activity Score in 28 joints; DMARDs: disease-modifying antirheumatic drugs; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-17i: interleukin 17 inhibitor; JAKi: Janus kinase inhibitor; LEF: leflunomide; MDA: minimal disease activity; mTSS: van der Heijde modified Total Sharp Score; MTX: methotrexate; NA: not available; PASDAS: Psoriatic Arthritis Disease Activity Score; PDE4i: phosphodiesterase type 4 inhibitor; PtGA: patient global assessment; SF-36 PCS: 36-item Short Form Health Survey physical component summary; SJC66: 66-joint swollen joint count; SSZ: sulfasalazine; TJC68: 68-joint tender joint count; TNFi: tumor necrosis factor inhibitor.

Table 2. Class of pharmacological treatments compared to standard of care/csDMARDs in patients refractory to csDMARDs.

Intervention	GRADE Evidence (Effect Size)															Recommendation	Consensus	
	MDA	PASDAS	ACR20	ACR50	ACR70	DAS28	DAPSA	SJC66/ TJC68	PtGA	Pain	HAQ-DI	SF-36 PCS	mTSS	AEs	Overall Evidence		Agreement Median (IQR)	Agreement ≥ 7/10 (%)
CyA	NA	NA	NA	NA	NA	NA	NA	NA	Low (ns)	Low (ns)	Low (ns)	Low (ns)	Low (ns)	Very Low (ns)	**Low** (ns)	**Conditional for**[a]	8.5 (7.0-9.0)	82.1
PDE4i	NA	NA	High (sup)	Moderate (sup)	Moderate (ns)	High (sup)	NA	High (sup)	High (sup)	High (sup)	Moderate (sup)	High (sup)	NA	Low (ns)	**Moderate to High** (sup)	**Strong for**	7.0 (6.0-8.0)	70.4
TNFi	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	High (sup)	NA	NA	NA	High (sup)	High (sup)	High (sup)	Moderate (sup)	Low (ns)	**High** (sup)	**Strong for**	10 (9.0-10.0)	100
IL-17i	High (sup)	NA	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Low (ns)	**High** (sup)	**Strong for**	10 (9.0-10.0)	100
IL-12/23i	NA	NA	High (sup)	High (sup)	Moderate (sup)	High (sup)	NA	NA	NA	NA	High (sup)	High (sup)	Low (ns)	Low (ns)	**Moderate to High** (sup)	**Strong for**	9.0 (8.0-10.0)	100
IL-23i	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	High (sup)	High (sup)	NA	Low (ns)	**High** (sup)	**Strong for**	9.0 (8.0-10.0)	100
JAKi	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	High (sup)	Moderate (sup)	Low (ns)	**High** (sup)	**Strong for**	9.0 (9.0-10.0)	100
CTLA4-Ig	Low (ns)	Low (ns)	Low (sup)	Low (sup)	Low (ns)	Low (sup)	Low (sup)	NA	NA	NA	Low (sup)	Low (sup)	NA	Low (ns)	**Low** (sup)	**Conditional for**[a]	9.0 (7.0-9.8)	82.1
Dual TNFi/ IL-17i	NA	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	NA	NA	NA	Moderate (sup)	NA	NA	Very low (ns)	**Moderate** (sup)	**Not making recommendation**[b,c]	10.0 (9.3-10.0)	100
IL-6i	NA	Very low (NT)	Low (sup)	Very low (NT)	Very low (NT)	Very low (NT)	NA	Very low (NT)	Very low (NT)	Very low (NT)	Very low (ns)	Very low (ns)	NA	Very low (ns)	**Very Low** (ns)	**Conditional against**[b]	9.5 (8.0-10.0)	96.4

Color coding for effect sizes: light green (sup): significantly superior to placebo or active comparator; light Amber (ns): no significant difference to placebo or active comparator; blue (NT): data reported only graphically, or no statistical test reported. [a]Reserve for no alternatives available. [b]Not approved by authorities. [c]Not available in the market. ACR20/50/70: American College of Rheumatology 20/50/70 response criteria; AEs: adverse events; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; CTLA4-Ig: cytotoxic T-lymphocyte-associated protein 4 antibody; CyA: cyclosporin A; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score in 28 joints; GRADE: Grading of Recommendations Assessment; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-17i: interleukin 17 inhibitor; JAKi: Janus kinase inhibitor; MDA: minimal disease activity; mTSS: van der Heijde modified total Sharp score; NA: not available; PASDAS: Psoriatic Arthritis Disease Activity Score; PDE4i: phosphodiesterase type 4 inhibitor; PtGA: patient global assessment; SF-36 PCS: 36-item Short Form Health Survey – physical component summary; SJC66: 66-swollen joint count; TJC68: 68-tender joint count; TNFi: tumor necrosis factor inhibitor.

It is acknowledged that PDE4i is not significantly different compared to usual care in achieving a high level of peripheral joint response (ACR70); this may be relevant when considering therapeutic choice. Once again, the general principle of ongoing assessment, treat-to-target, and appropriate escalation of therapies would apply. The evidence to support CTLA4-Ig is low, but we conditionally recommended it for situations when no alternative is available.

Concerning the choice of bDMARDs, 2 head-to-head RCTs with IL-17i[20,21] and 1 RCT with a JAKi[13] were powered to compare efficacy with adalimumab (ADA). One RCT with a JAKi[22] included ADA as a comparison arm, but it was not statistically powered to compare differences in efficacy between the JAKi and ADA. A moderate-to-high level of evidence of equivalent efficacies of IL-17i and JAKi compared to TNFi were demonstrated (Table 3). In the head-to-head RCT with JAKi, high-dose (30 mg daily) upadacitinib demonstrated superiority over ADA for ACR20 at the primary endpoint with a moderate-to-high level of evidence,[13] whereas upadacitinib at a dose of 15 mg daily was noninferior compared to ADA in all outcomes. Superiority over TNFi was not seen for lower-dose upadacitinib and the other JAKi.[22,23] The working group agreed on equally recommending IL-17i and JAKi with TNFi for active peripheral arthritis in patients with inadequate response to csDMARDs (agreement 92.9% and 92.9%, respectively). There is no head-to-head study comparing IL-23i with other bDMARDs. Based on the moderate-to-high level of evidence supporting superiority of IL-23i over standard care for patients both with or without prior experience with bDMARDs,[24,25] the working group conditionally recommended IL-23i as another bDMARD (agreement 89.3%). One small open-label study comparing the efficacies of IL-12/23i with TNFi found no superiority of IL-12/23i in peripheral joint domain.[26] With this very low level of evidence, the working group conditionally recommended IL-12/23i compared to other bDMARDs for patients with inadequate response to csDMARDs (agreement 89.3%).

Recommendations for patients with inadequate response to bDMARDs. Patients recruited to different RCTs were heterogenous in terms of prior experience to bDMARDs and inadequate response to bDMARDs. No study differentiated primary from secondary failure to bDMARDs. As a result, the evidence derived can only be applied to patients who have had prior experience with bDMARDs. There is a moderate-to-high level of evidence to support superiority of a second TNFi, IL-17i, IL-23i, or JAKi over continuing usual care with or without csDMARDs. The working group strongly recommended these therapeutic options (agreement 92.9-100%; Table 4). There is a low level of evidence to support IL-12/23i being superior to continued usual care. The working group conditionally recommended IL-12/23i (agreement 96.4%). As for PDE4i, in patients who had prior experience to bDMARDs, there is a moderate level of evidence supporting its superiority compared to continuing usual care, and the working group conditionally recommended it (agreement 78.6%). However, in patients who had inadequate response to bDMARDs, there is a moderate level of evidence showing PDE4i is not significantly different from continuing usual care; therefore, treatment choices other than PDE4i should be considered. Similarly, we conditionally recommended CTLA4-Ig (agreement 85.7%).

Recommendations for nonpharmacological interventions. The working group reviewed data for various nonpharmacological interventions from 6 RCTs. Owing to a very low level of evidence supporting these interventions as being superior to their respective controls (Supplementary Material 6, available with the online version of this article), no recommendations could be made. A special working group consisting of 4 rheumatologists, 2 PRPs, and 1 moderator was formed to address nonpharmacological managements. The group discussed the evidence in a webinar and proposed the following recommendations regarding exercise, diet, and smoking cessation.

Physical activity can reduce body weight, risk of diabetes mellitus, and risk of cardiovascular (CV) diseases. The benefit of physiotherapy has been demonstrated in patients with other arthritis such as axial spondyloarthritis. Although it was not possible to recommend any specific type of exercise over another, the working group conditionally recommended exercise or physical activity as means to improve general health, reduce obesity, and risk of CV diseases. Physiotherapy or exercising are not treatments for active peripheral arthritis per se but should be used as an integral part of the general management of PsA, especially when active arthritis is stabilized. The entire working group voted on the above statements (response rate 90%) and an agreement of 96.4% was achieved. The working group acknowledged that improvements in study design may also help to better understand the benefits of exercise, including, but not limited to, randomization and blinding procedures, standardizing protocols, adequacy of sample size, and targeting certain patient subgroups.

Weight reduction reduces the load on the weight-bearing joints and is associated with lower disease activity.[27-29] A healthy diet is beneficial in reducing CV risk. The working group conditionally recommended a healthy diet aiming at preventing weight gain and/or weight loss (agreement 96.4%). Again, no specific diet could be recommended over another.

Smoking is associated with increased CV risk. The literature is controversial as to whether smoking may increase the risk of PsA or worsen disease activity,[30] but there is some evidence that smoking reduces chemotactic activity of monocytes and reduces inflammation at the molecular level.[31] The working group conditionally recommended smoking cessation to reduce CV risk for all patients with PsA (agreement 96.4%; data not shown).

DISCUSSION

We conducted an updated evidence review to inform optimal treatment for the peripheral arthritis domain in PsA. The evidence supporting treatment for other domains are addressed by separate GRAPPA working groups. We derived the level of certainty of evidence to support each class of treatment using the GRADE method,[9] followed by consensus on the recommendations for patients who were treatment naïve or had inadequate response to csDMARDs or bDMARDs. The study group also made recommendations for nonpharmacological interventions, including exercise, healthy diet, and smoking cessation. This

Table 3. Class of pharmacological treatments compared to TNFi in patients with prior experience with csDMARDs.

Intervention	GRADE Evidence															Recommendation	Consensus	
	MDA	PASDAS	ACR20	ACR50	ACR70	DAS28	DAPSA	SJC66/ TJC68	PtGA	Pain	HAQ-DI	SF-36 PCS	mTSS	AEs	Overall Evidence		Agreement Median (IQR)	Agreement ≥ 7/10 (%)
PDE4i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**	–	–
IL-17i	Low (sup)	Moderate (ns)	High (ns)	High (ns)	High (ns)	Moderate (sup)	Moderate (sup)	Low (ns)	Low (ns)	Low (ns)	High (ns)	Low (ns)	Very Low (ns)	Low (ns)	**Moderate** (for similar efficacies)	**Equal strong recommendation for IL-17i vs TNFi**	9.0 (8.0-10.0)	92.9
IL-12/23i	Very Low (ns)	NA	NA	NA	NA	Low (ns)	NA	Low (ns)	NA	NA	NA	Very Low (ns)	NA	NA	**Very Low** (for similar efficacies)	**Conditional recommend IL-12/23i over TNFi**	9.0 (7.0-9.0)	89.3
IL-23i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**Conditional recommend for IL-23i vs TNFi** (extrapolating from superiority of IL-23i vs PCB)	8.0 (7.3-10.0)	89.3
JAKi	High (sup)	NA	High (sup)	High (sup)	High (sup)	Moderate (ns)	NA	Moderate (ns)	Moderate (ns)	Moderate (sup)	High (sup)	Moderate (ns)	Low (ns)	Low (ns)	**Moderate to high** (for similar efficacies)	**Equal strong recommendation for JAKi vs TNFi**	9.0 (8.0-10.0)	92.9
CTLA4-Ig	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**	–	–
Dual TNFi/ IL-17i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**	–	–
IL-6i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**	–	–

Color coding for effect sizes: light green (sup): significantly superior to placebo or active comparator; light amber (ns): no significant difference to placebo or active comparator. ACR20/50/70: American College of Rheumatology 20/50/70 response criteria; AE: adverse event; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CTLA4-Ig: cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score in 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-17i: interleukin 17 inhibitor; JAKi: Janus kinase inhibitor; MDA: minimal disease activity; mTSS: van der Heijde modified total Sharp score; NA: not available; PASDAS: Psoriatic Arthritis Disease Activity Score; PDE4i: phosphodiesterase type 4 inhibitor; PtGA: patient global assessment of Disease Activity; SF-36 PCS: 36-item Short Form Health Survey physical component summary; SJC66: 66-joint swollen joint count; TJC68: 68-joint tender joint count; TNFi: tumor necrosis factor inhibitor.

Table 4. Class of pharmacological treatments compared to standard of care/csDMARDs/placebo in patients with prior experience with bDMARDs.

Intervention	GRADE Evidence															Recommendation	Consensus	
	MDA	PASDAS	ACR20	ACR50	ACR70	DAS28	DAPSA	SJC66/ TJC68	PtGA	Pain	HAQ-DI	SF-36 PCS	mTSS	AEs	Overall Evidence		Agreement Median (IQR)	Agreement ≥ 7/10 (%)
PDE4i	NA	NA	Moderate (bDMARD exp) (sup) Moderate (bDMARD IR) (ns)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Very Low (ns)	**Low** (sup)	**Conditional for**	8.0 (7.0-9.0)	78.6
TNFi	NA	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	NA	NA	NA	NA	Moderate (sup)	Moderate (sup)	Low (ns)	Very Low (ns)	**Moderate** (sup)	**Strongly recommend for a 2nd TNFi**	9.0 (8.0-10.0)	92.9
IL-17i	Moderate (sup)	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	High (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	High (sup)	High (sup)	Very Low (sup)	Low (ns)	**Moderate to high** (sup)	**Strong for**	10.0 (9.0-10.0)	100
IL-12/23i	NA	NA	Low (NT)	NA	NA	NA	NA	NA	NA	NA	Moderate (sup)	NA	NA	Low (ns)	**Low** (sup)	**Conditional for**	8.0 (7.3-9.0)	96.4
IL-23i	NA	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	NA	NA	NA	NA	NA	NA	NA	Very Low (ns)	**Moderate** (sup)	**Strong for**	9.0 (8.0-10.0)	96.4
JAKi	Moderate (sup)	NA	Moderate (sup)	Moderate (sup)	Moderate (sup)	Moderate (sup)	NA	High (sup)	Moderate (sup)	High (sup)	High (sup)	High (sup)	NA	Very Low (ns)	**Moderate to High** (sup)	**Strong for**	9.0 (8.0-10.0)	100
CTLA4-Ig	NA	NA	Moderate (sup)	Moderate (ns)	Moderate (ns)	NA	NA	NA	NA	NA	Moderate (ns)	Moderate (ns)	NA	Very Low (ns)	**Moderate** (sup)	**Conditional for**[a]	8.0 (7.0-9.8)	85.7
Dual TNFi/ IL-17i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**Not making recommendation**	–	–
IL-6i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**Not making recommendation**	–	–

Color coding for effect sizes: light green (sup): significantly superior to placebo or active comparator; light amber (ns): no significant difference to placebo or active comparator; blue (NT): data reported only graphically, or no statistical test reported. [a]Reserve for no alternatives available. ACR20/50/70: American College of Rheumatology 20/50/70 response criteria; AE: adverse event; bDMARD: biologic disease-modifying antirheumatic drug; bDMARD exp: biological DMARD experienced; bDMARD IR: biological DMARD inadequate response; CTLA4-Ig: cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score in 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-17i: interleukin 17 inhibitor; JAKi: Janus kinase inhibitor; MDA: Minimal Disease Activity; mTSS: van der Heijde modified total Sharp score; NA: not available; PASDAS: Psoriatic Arthritis Disease Activity Score; PDE4i: phosphodiesterase type 4 inhibitor; PtGA: patient global assessment of Disease Activity; SF-36 PCS: 36-item Short Form Health Survey physical component summary; SJC66: 66-joint swollen joint count; TJC68: 68-joint tender joint count; TNFi: tumor necrosis factor inhibitor.

work represented a concerted effort among stakeholders from 5 continents, including clinicians and PRPs; and provided information for the development of the 2021 updated GRAPPA treatment recommendations.

Since the last GRAPPA recommendations,[5] there remains a low level of certainty of evidence to support the use of csDMARDs for the treatment of peripheral arthritis. In contrast, there are new data with a high level of certainty to support the use of TNFi being superior to placebo, particularly as first-line treatment in patients with early disease.[16,17] However, besides the quality of evidence, other factors including values, preference, and accessibility/costs are equally important for determining the strength of the recommendations.[9] Given the good response from observational data and long-observed clinical responses, csDMARDs as first-line treatment is still recommended. However, it is important to acknowledge the high-quality of evidence supporting TNFi as first-line treatment. The decision will be at the discretion of a shared decision-making process between the clinician and the patient, with the individual's risks, benefits, and access to medications being considered.

Compared to the previous GRAPPA recommendations, we now have high-quality evidence supporting TNFi, IL-17i, IL-23i, and JAKi being superior to placebo, particularly for patients with inadequate response to csDMARDs and bDMARDs. These treatment options are all now strongly recommended compared to conditionally recommended in the previous GRAPPA recommendations.[5] Similarly, a moderate-to-high level of certainty of evidence supports IL-12/23i or PDE4i being superior to placebo in patients with inadequate response to csDMARDs, but with smaller effect sizes for peripheral arthritis. Therefore, we strongly recommended IL-12/23i or PDE4i for csDMARD inadequate responders but only conditionally recommended them for bDMARD inadequate responders. For all RCTs we reviewed for PDE4i, TNFi, IL-17i, IL-12/23i, IL-23i, and JAKi, there were no differences in efficacy in the subgroups of patients with or without concurrent csDMARDs compared to placebo. In the Seam-PsA study, which was adequately powered to compare MTX, TNFi, and the combination, there was no difference in efficacy between the TNFi monotherapy arm and the TNFi/MTX combination arm.[17] These findings support that a combination of csDMARD with bDMARD or JAKi may not be necessary to achieve short-term responses. However, for those who failed csDMARDs, the shared decision to add on vs switch over to a bDMARD or a JAKi would be at the discretion of the doctor and patient. Concerning the choice between different bDMARDs or tsDMARDs, there were only 2 head-to-head RCTs comparing IL-17i with TNFi[20,21] and 1 trial comparing JAKi with TNFi[13] that were adequately powered to inform optimal therapeutic choices. Based on current evidence, the efficacies of IL-17i and TNFi are comparable for the peripheral arthritis domain in those with an inadequate response to csDMARDs. Superiority for JAKi given at a higher dose over TNFi in some peripheral arthritis outcomes, but not all, was seen from a single RCT.[13] Consistency for other JAKi and longer-term safety is yet to be shown, and therefore the working group would not recommend one class of drug over the other.

We acknowledge some limitations of this systematic literature review. The evidence derived was based on patients with PsA predominantly with polyarthritis, with evidence extrapolated to those with oligoarthritis. Recommendations endorsed were based mainly on efficacy compared to placebo; there are very few head-to-head studies comparing efficacy of the different therapeutic agents. For inadequate responders, there are insufficient data for specific recommendations based on primary vs secondary failure to prior treatment.

In conclusion, we present this work from a systematic effort of relevant rheumatologists with interest in PsA and PRPs from 5 continents. We have summarized the updated evidence review and achieved consensus on recommendations for the available therapeutic options for the treatment of the peripheral arthritis domain of PsA. This work supports the development of the updated 2021 GRAPPA treatment recommendations for PsA.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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