The updated GRAPPA and EULAR recommendations for the management of psoriatic arthritis: similarities and differences

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Key words

Psoriatic arthritis, psoriasis, patient, recommendations, management, EULAR, GRAPPA

Grants: none

Competing interests:

The authors declare a potential conflict of interest having received grant support and/or honoraria for consultations and/or for presentations as indicated:

LC Coates: LCC has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB; and has been paid as a speaker for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Medac, Novartis, Pfizer and UCB.

L Gossec: research grants: Amgen, Galapagos, Lilly, Pfizer, Sandoz, UCB; consulting fees: AbbVie, Amgen, BMS, Celltrion, Galapagos, Gilead, GSK, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, UCB.

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Running title

Recommendations for management of PsA

Introduction

Management recommendations are helpful for clinicians and patients because they provide guidelines for the use of medications.[1] In psoriatic arthritis (PsA), several recommendation sets have been developed: these include the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recommendations.[2-4] However, such recommendations must be regularly updated, especially when drugs are frequently developed, as is the case in PsA (**Figure 1**).[5, 6] Over the past 2 years, both EULAR then GRAPPA presented updated PsA treatment recommendations integrating the most recent treatment options.[7, 8] In both, the heterogeneity of PsA is recognized and the place of various drugs in the therapeutic armamentarium is discussed (**Figure 2**). Such agents include conventional disease modifying antirheumatic drugs (csDMARDs), such as methotrexate, and targeted therapies including biologics (bDMARDs) and targeted synthetic drugs (tsDMARDs). The proposed sequential use of these drugs, as well as some other aspects, differ between the two sets of recommendations (**Figure 2)**.

This editorial provides comments on the main similarities and differences between the recommendations, also considering changes from the previous versions in 2016.[9, 10] We will discuss (a) the focus, (b) methodology, (c) underpinning data analysed and (d) the presentation of the recommendations.

1- Focus of the recommendations

Both recommendation sets focus on PsA, and do not refer to other forms of spondyloarthritis, contrary to some other recommendation sets such as the recently updated Franch recommendations.[11] The difference in approach is evidenced again in these updates, with a greater focus on psoriasis in the GRAPPA recommendations (**Table 1**).[2, 8] This difference is related to the organisation's missions. GRAPPA is a global research group dedicated to both psoriasis and PsA. (http://www.grappanetwork.org/) On the other hand, EULAR is aimed at healthcare professionals (including rheumatologists) dealing with rheumatic diseases, with a European focus although recommendations are designed to be applicable internationally[3] (http://www.eular.org/recommendations_home.cfm). Thus, the EULAR recommendations are centred on musculoskeletal manifestations with discussion around co-management with a dermatologist as appropriate, whereas the GRAPPA

recommendations are centred on both musculoskeletal and dermatological manifestations. However, both recommendations groups included dermatologists and patient research partners.

In 2015, GRAPPA added a specific recommendation working group related to comorbidities of PsA. Whilst this went beyond the rheumatology and dermatology focus, it was felt to be important given the impact of comorbidities in PsA. With the latest update, GRAPPA decided to split this domain into two groups: related conditions (uveitis and inflammatory bowel disease [IBD]) and comorbidities. The recommendations do not provide full guidance on the management of IBD and uveitis, but do include recommendations for all relevant drugs used for PsA and whether these drugs are recommended or relatively contraindicated in people with co-existent IBD or uveitis. These are now included in the main recommendations figure.[8]

2- Methods applied to develop the recommendations

Both recommendation sets are evidence-based but the interpretation of the literature differs. The EULAR recommendations used the Oxford Centre for Evidence Based Medicine levels of evidence from 1a to 4, to assess the level of evidence [7]. In contrast, GRAPPA changed to utilising the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [8] from 2015 onwards. Both are internationally recognised methodologies to assess the evidence but follow different processes. A key difference is that GRADE separates the evidence effect estimates from the strength of the subsequent recommendation, allowing recommendation groups to take into account a wide range of other attributes. This difference in the assessment of the literature may explain some divergences between recommendations.

EULAR followed the updated EULAR standard operating procedures to develop this update.[12] For updates, EULAR mandates that changes be made only if there is a strong consensus that a change is necessary. Thus, the taskforce met (physical meeting, pre-Covid era) and discussed the recommendations, and potential changes to be made. The recommendations were then sent for online anonymous voting on level of agreement, to the taskforce members who had developed the recommendations.

In the development of the GRAPPA recommendations, recommendations for/against medications were developed initially in domain groups (peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis and nail disease) and then finalised within the wider working

group. Domain groups were led by experts in the field but all members of GRAPPA were invited to join a working group. Given the COVID-19 pandemic, all interactions were virtual. Following development, the draft recommendations were sent to all GRAPPA members for online consensus voting with 170 respondents.

In both cases, participants in the voting process for agreement can be considered as experts on PsA since the EULAR taskforce membership but also the GRAPPA membership are selective processes.

3- Trials included and analysed in the development of the recommendations

In both cases (EULAR and GRAPPA), the recommendations are based on systematic literatures updates. The EULAR recommendations update reviewed publications from 2015-2018, where the more recent GRAPPA recommendations also included studies published in 2019-2020. [8, 13]

Whilst methotrexate is recommended by both groups for peripheral arthritis, additional data provided by the SEAM-PsA study in 2019 [14] has resulted in its inclusion within GRAPPA recommendations for enthesitis and dactylitis. Although this study was not placebo-controlled, it did show improvements in both domains with methotrexate monotherapy (SPARCC enthesitis score reduced by 3.1 with methotrexate monotherapy compared to 3.0 with etanercept monotherapy; Leeds dactylitis index score reduced by 128.8 with methotrexate monotherapy compared to 119 with etanercept monotherapy) with no significant difference seen between methotrexate and etanercept treated groups. This resulted in a conditional recommendation in the GRAPPA algorithm, for methotrexate in enthesitis and dactylitis.

Both recommendation sets propose that bDMARDs targeting IL-23 by inhibiting the p19 subunit could be used in PsA.[7, 8] The EULAR recommendations refer to this drug class, pooled together with the IL-12/23 drug ustekinumab, which was available (approved by EMA in 2013) before the EULAR update (**Figure 1**). GRAPPA included in their analysis, additional data on guselkumab,[15, 16] and risankizumab which have proven efficacy in peripheral arthritis, enthesitis and dactylitis resulting in their inclusion in the GRAPPA recommendations (**Figure 2**). However, there remains controversy about the efficacy of these drugs in axial disease. There are negative trials published in ankylosing spondylitis but improvements in axial patient reported outcome measures such as the Bath ankylosing spondylitis disease activity index (BASDAI) seen in PsA trials. This has led to the proposal of specific studies in axial PsA. This would follow the only large, randomised trial in axial PsA which tested

secukinumab, an IL-17A inhibitor versus placebo.[17] Currently, given the contrary data, IL-23 inhibitors are not recommended for axial PsA, in either recommendation set.

At the time of the EULAR recommendations, the only licensed janus kinase (JAK) inhibitor was tofacitinib which had to be prescribed in combination with methotrexate (**Figure 1**). Given the limited long-term safety available for JAK inhibitors at that time, they were reserved as second line targeted therapies. Since that time, upadacitinib (a more selective JAK1 inhibitor) has been licensed for PsA following phase 3 trials [18, 19] and preliminary data is available for deucravacitinib (a tyrosine kinase inhibitor). [20] In the GRAPPA recommendations, JAK inhibitors are recommended in multiple domains of PsA, at the same level as bDMARDs in most cases (**Figure 2**). However, the encouraging efficacy data of JAK inhibitors must be balanced by recent safety concerns published after the literature review periods for both recommendations in the ORAL-Surveillance study. This study failed to meet its primary outcome of non-inferiority for cardiovascular risk and malignancy when tofacitinib was compared to TNF-alpha inhibitors in patients with rheumatoid arthritis (RA), who were either over 50 or who had a baseline cardiovascular risk factor.[21] Further research is required to identify the relative risk in patients with PsA and to help identify patients who are or are not suitable for treatment with JAK inhibitors.[22]

4- Presentation of the recommendations

In the 2019 update, the EULAR flowchart presents more clearly treatment options for peripheral arthritis (poly/oligo/monoarthritis), enthesitis and predominant axial disease.[7] Here the enthesitis and axial domains are separate and follow a very similar approach to those domains in the GRAPPA recommendations. As mentioned above, the key difference is the inclusion of methotrexate for enthesitis, in the GRAPPA recommendations.

In 2019, the EULAR recommendations made a decision to split the recommendations for peripheral arthritis into polyarthritis (>4 joints) and mono/oligoarthritis, emphasising that polyarthritis is a recognised poor prognostic factor in PsA. The medications recommended for treatment of peripheral arthritis are identical, but the presence of polyarthritis is used to identify those requiring rapid disease-modifying treatment. The EULAR recommendations also provide a greater focus on the use of a treat-to-target approach[23] with this being the first recommendation listed. GRAPPA only covers this within the overarching principles discussing treatment aiming at a “goal of therapy”.

There remains limited evidence on the best management of comorbidities in PsA patients. However, comorbidities are a frequent issue for patients with PsA and commonly impact on treatment selection.[24, 25] GRAPPA have included a table to highlight potential interactions between comorbidities and treatment choice including therapies where there should be cautions or contraindications to their use. [2, 8]

There is very limited evidence in the literature to support the order in which medications should be used. This introduces more variability into the recommendations, as different factors influence recommendations on this point. In GRAPPA, csDMARDs, bDMARDs and tsDMARDs are recommended equally without any clear order where there is evidence for their efficacy. The SEAM study did show that a bDMARD (etanercept) had superior efficacy to methotrexate, potentially arguing for their recommendation as first-line agents as highlighted in the ACR 2018 recommendations. [4] As GRAPPA is an international organisation, all drugs were recommended given the limited amount of comparative evidence and to allow physicians to make appropriate choices depending on their healthcare settings.

In the EULAR recommendations, there is a clear “step up” approach where at least one csDMARD (usually methotrexate) is recommended before bDMARDs or tsDMARDs, for peripheral arthritis. This decision was based on the literature but also on expert opinion, considering efficacy data, tolerance and costs, but also long-term use of csDMARDs. EULAR also aims at guiding clinicians in their choices, whereas GRAPPA aims at being less prescriptive. A similar pattern is repeated in the potential prioritisation of targeted therapies in the recommendations. The recent recommendations considered the publication of the first head-to-head studies comparing targeted therapies in PsA, but none have shown a significant difference in efficacy in arthritis. [26, 27] There is however some evidence for differential efficacy in axial disease (as discussed earlier) and in psoriasis.[28-30] For that reason, the GRAPPA algorithm lists the drugs as a group without any ranking, but with some information about differentiation given in the text. In the EULAR recommendations, a contrario, bDMARDs are recommended over JAK inhibitors or apremilast. In the EULAR update, all 3 categories of biologics (targeting TNF-alpha, IL-17 and IL-23) are put at the same level.[7] However, in case of relevant skin involvement, IL-17 and IL-23 inhibitors are recommended rather than TNF inhibitors.

Conclusion

Regular updates to treatment recommendations are driven by the ongoing expansion in therapeutic options and research which means that recommendations become outdated

relatively quickly. The latest updates of the EULAR and GRAPPA treatment recommendations still differ somewhat in scope and output but show more similarities than differences as they are both underpinned by the same evidence-based approach. The implementation of these recommendations should benefit patients with PsA.

13Table 1 – domains covered by the recently updated GRAPPA and EULAR recommendations for the management of PsA

Domain	Eular	Grappa
Peripheral joint	yes	yes
Oligo vs polyarticular involvement	yes	No
Enthesitis	yes	yes
Dactylitis	yes	yes
Skin psoriasis	No	yes
Nail psoriasis	No	yes
IBD	No	yes
Uveitis	No	yes

IBD: inflammatory bowel disease

Figure 1 – timeline of drug authorisations in PsA

Figure 2. A comparison of drug algorithms for peripheral arthritis in the EULAR and GRAPPA recommendations

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