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**GRAPPA Treatment Recommendations: 2021 Update**

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**ABSTRACT**:One of the central missions of GRAPPA, since its inception, has been the development of treatment recommendations for patients with psoriatic arthritis (PsA). The initial guidelines, developed in 2009, were updated in 2015. Because of the abundance of new data concerning the therapeutic approach to PsA, GRAPPA members have been working throughout 2020-2021 to once again update the recommendations At the GRAPPA 2021 annual meeting, the full committee presented proposals from each of the treatment domain groups, including the comorbidities and related conditions groups, based on previous systematic literature reviews. Overarching principles and summary evidence tables were presented including results from a GRAPPA membership survey of patients and clinicians to assess levels of agreement. A draft final figure for the treatment recommendations was presented and discussed with the wider membership.

**Key Indexing Terms**:Psoriasis, Psoriatic Arthritis, GRAPPA, Treatment Recommendations

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**Word Count**:

Significant advances in novel therapies and new evidence on treatment strategies in PsA necessitate regular updates to treatment recommendations. The first iteration of the GRAPPA treatment recommendations were in 2009.1 In 2019, GRAPPA started the process to update the 2015 GRAPPA treatment recommendations 2 and these are now being finalised. Importantly, the methods underlying what is generally considered optimal guideline development have evolved over the years since the original guidelines were developed. Most newer iterations of treatment recommendations have adopted methods such as GRADE to ensure a transparent approach to grading the evidence underpinning recommendations.

**Underpinning evidence review**

A wide-ranging evidence review was commissioned to support the development of the new recommendations. This aimed to update the literature from 2013 onwards, that being the latest data used for the 2015 guidelines2. The systematic searches and methodology aiming to identify randomised controlled trial (RCT) data across multiple domains of PsA have previously been reported3.

Additional searches were completed for the two groups addressing conditions commonly associated with PsA (i.e. inflammatory bowel disease [IBD] and uveitis) as well as for comorbidities. These searches were more wide-ranging given the lack of RCTs in this area and addressed: i.) treatment options in patients with PsA and comorbidities, focusing on non-randomised controlled studies, cohort studies and pre-post studies. ii.) RCTs of individuals with IBD or uveitis treated with pharmaceutical drugs used in PsA. iii.) screening of comorbidities and related conditions in PsA (including not only RCTs, but also non-randomised trials as well as pre-post, cohort, case-control, cross-sectional analyses). iv.) prognosis and phenotype of individuals with PsA and related conditions (cohort studies, RCTs, case-control, cross-sectional studies)

**Overarching principles and additional guidance statements**

Overarching principles for the management of people with PsA were included in the 2015 version of the GRAPPA recommendations. These have been updated incorporating new evidence-based principles and experience-based approaches for goals of treatment. One additional overarching principal has been included to highlight the optimal role of the recommendations within a shared decision making approach. Two additional position statements were added, covering the topics of biosimilars and tapering therapy with considerations across all disease treatment domains. In May 2021, the overarching principles and guidance statements were circulated to the wider GRAPPA membership for agreement voting. High levels of support (>80% in most cases) were identified both from patient research partners and from GRAPPA clinicians.

**Development of the evidence table and treatment recommendations figure**

Following the evidence review, all of the individual domain groups contributed to a summary evidence table. This followed a GRADE format resulting in strong/conditional recommendations either for or against a drug. This was developed with consensus across all group leaders.

Several key considerations were implemented across groups to facilitate consistency of approach:

1. Individual drugs with an ostensibly shared mechanism of action would be considered as a group unless there was solid evidence for within-class differences (e.g. the 5 distinct inhibitors of TNF are groups as ‘TNF inhibitors’; with evidence based differences called out – such as the inefficacy of etanercept in IBD). In the future, additional data may warrant separation of agents currently considered to be within a group.
2. The primary goal methodologically was to use data from PsA studies. However, for some domains, such as uveitis and IBD, the majority of the data come from studies outside of PsA; in those cases, that was the source of the data. For other domains, such as axial arthritis and skin psoriasis and nail psoriasis, there was a mixture. For some agents, e.g TNF inhibitors, there is abundant data specifically in PsA whereas for other mechanisms of action, most data were not from PsA studies and hence were extrapolated
3. The goal of these recommendations is NOT to be primary recommendations for the treatment of these associated conditions (e.g. IBD) but rather to serve as a resource for consideration of approaching active disease within these domains for PsA patients.
4. As GRAPPA guidelines are international, and as regulatory approvals can vary substantially in different jurisdictions, specific licensing or regulatory language from any individual area were not considered to be ‘evidence’; data from the published research trials formed the basis of the recommendations.

**Discussion at the 2021 meeting**

Following presentation from each of the domain sub-groups, the proposed summary evidence table and figure were presented for discussion. Questions were invited from GRAPPA members and answered by the committee:

* **Is there parity where multiple drugs are recommended?**

In the figure and summary table, drugs with positive evidence in that particular domain of disease are recommended. These are not listed in any particular order. There is limited evidence comparing therapies in PsA, but in certain domains head-to-head trials have shown superiority for one drug over another. In this case, further information will be given in the text to guide therapeutic decisions.

* **Why are JAKi equally recommended for axial disease when evidence for axPsA AND axSpA are limited?**

As noted, individual drugs with an ostensibly shared mechanism of action would be considered as a group in the absence of solid evidence for within-class differences There is now one large RCT addressing axial PsA specifically with one jakinib, but much of the recommendation still extrapolates from studies in AS or AxSpA.

* **What types of psoriasis do the recommendations address?**

The recommendations for skin psoriasis refer specifically to plaque psoriasis, as there is a paucity of data on other psoriasis phenotypes (e.g. pustular psoriasis) in the PsA studies that were included in the literature review.

* **Why are corticosteroids not included in treatment of uveitis?**

As noted the goal of these recommendations is not to be primary recommendations for the treatment of associated conditions such as uveitis but rather to serve as a resource for consideration of approaching active disease within the domain among PsA patients.. We would always recommend that management of related conditions should be led by appropriate specialists.

* **How do you propose that we treat patients who present with multiple domain involvement?**

This speaks to the core principle of the figure; namely a clinician using these recommendations should fully assess disease activity across individual domains as well as to ascertain their impact to a given individual. Then clinicians can identify which drugs are efficacious in those particular domains, and provide this information to the patient. Importantly, in addition to efficacy across domains, the presence of or concern for comorbid conditions may certainly impact the choice of any specific therapy. As in the 2015 recommendations, there is a plan to include case studies to demonstrate this in practice.

* **Will there be any recommendation on concomitant MTX with biologics?**

Discussion around concomitant csDMARD use alongside biologics is not included in the table or figure but will be covered in the text of the recommendations. Since 2015, additional data are available on the use of concomitant DMARDs for efficacy (e.g. the SEAM-PsA study) and for persistence of TNF inhibitors specifically (from registry data).

* **Will there be any distinction between primary and secondary inefficacy for selection of second line therapy?**

Again, this will be discussed in the text, although limited data exist, particularly in RCTs and there is no clear definition of primary and/or secondary failure. While the concepts seem straightforward, in reality ‘failure’ of any treatment can be much more complex, with consideration of efficacy across various domains over time, tolerability issues, and exogenous factors such as cost.

* **Any recommendations on measuring drug trough levels?**

Therapeutic Drug Monitoring (TDM) has risen as a topic of consideration, particularly in Gastroenterology. However, the limited data published to date do not support its regular use in PsA.

* **Is there a plan to update the PRP treatment recommendations? Have people used the previous document with their patients?**

The clinicians on the panel replied in the affirmative that they had used the previous iteration of the document in clinic. In the UK, a number of these were printed with pharmaceutical support and have been distributed to key clinics. The patient representative (DO) replied that he was keen to update the PRP treatment recommendations in parallel with the main recommendations.

**Summary**

GRAPPA is currently finalising domain specific recommendations with an aim to produce updated treatment recommendations for publication in 2021. These follow a GRADE-informed methodology to update recommendations taking account of the strengths and limitations of the evidence base. There has been strong agreement with the recommendations identified on GRAPPA membership polls throughout development.

**References**

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