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Title: New GRAPPA and EULAR recommendations for the management of psoriatic arthritis: process and challenges faced

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Running title

EULAR and GRAPPA recommendations for management of PsA

Introduction

In 2015, both the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European League Against Rheumatism (EULAR) presented updated recommendations on the management of psoriatic arthritis (PsA)[1, 2]. New therapies, assessments and increasing evidence on comorbidities required substantial revision of treatment strategies.

This editorial provides comments on the key barriers faced and how these were addressed.

Key challenges faced

The challenges focus around (a) the remit of the recommendations, (b) the scope of the literature review and (c) assessment of the available data (Table 1).

A. Remit and Presentation of Recommendations

A difference in approach is clear from the mission of the organisations. GRAPPA is a global research group dedicated to both psoriasis and PsA.(http://www.grappanetwork.org/) Obviously, EULAR concentrates on rheumatic diseases with a European focus although recommendations are designed to be applicable internationally[3] (http://www.eular.org/recommendations_home.cfm). GRAPPA assessed both dermatological and musculoskeletal manifestations with dermatologists leading groups focused on skin and nail disease. The EULAR recommendations focused specifically on musculoskeletal PsA with referral to a dermatologist recommended for patients with significant skin disease but no management recommendations for skin or nail manifestations.

1. Heterogeneity of PsA

To address heterogeneity, . both groups assessed efficacy of therapies for different domains of disease. GRAPPA presented the full data in 6 distinct algorithms according to predominant phenotype allowing physicians to pick an optimal therapy based on disease activity in each domain. Given their remit, the GRAPPA recommendations include therapies for skin and nail disease in addition to musculoskeletal involvement. EULAR developed a single algorithm focussed on peripheral arthritis with different pathways for enthesitis and axial disease.

To address the frequent comorbidities of PsA, the GRAPPA recommendations included recommendations based on a specific systematic literature review (SLR) including both extra-articular SpA manifestations and distinct comorbidities such as cardiovascular disease, metabolic syndrome, depression, and skin cancer[4]. EULAR placed comorbidities to the forefront in the overarching principles but without an SLR or any specific recommendations.

2. Stakeholder involvement

Patients Involvement

Both organisations involved patient representativesto ensure better representation of patients' needs and uncertainties, and prevent a mismatch between their preferences and the scientific focus in research.[5] [6]Proper representation is key because the personal experience of a patient will likely strongly influence their view. Patients in both organisations, with specific training/support, participated in development of overarching principles and recommendations discussing the evidence presented. The development of lay summaries drafted specifically for patients is currently underway.

Consensus process within membership

Drafting of the GRAPPA recommendations was guided by a steering committee but appraisal of the evidence and generation of treatment recommendations was completed in specific domain subcommittees with regular feedback to the GRAPPA membership. Drafts were disseminated to members, including patient research partners to allow feedback before 145 participants voted on agreement.

The EULAR steering group defined the systematic literature reviews (SLR) scope. Following this, the findings of the SLR were discussed within a Taskforce, consisting of 34 people: 28 rheumatologists, 3 people affected with PsA, 2 health professionals and 1 dermatologist. There were some subsequent small modifications prior to voting on agreement by Taskforce members.

B. Scope of the systematic literature review to collect trial data used as basis for the recommendations

Both sets of recommendations were based on large SLRs to provide the evidence base including randomised controlled trials and data from conference abstracts. This decision to include abstracts was controversial but it was taken to ensure that the recommendations were not outdated rapidly. New therapies with data predominantly in abstract form only were included in both recommendations. These were clearly demarcated as conditional in the GRAPPA recommendations but no order was suggested within the biologics allowing flexibility depending on the details of the case. EULAR considered all data, regardless of full-text publication status. These new therapies were included but were suggested as second line biologics as they had less accumulated experience and safety data.

C. Assessing the evidence

1. Assessment quality

The EULAR recommendations used the Oxford Centre for Evidence Based Medicine levels of evidence from 1a to 4 [7]. In contrast, GRAPPA adapted the newer Grading of Recommendations Assessment, Development and Evaluation (GRADE) in the latest update[8]. GRADE gives recommendations following assessment of desirable and undesirable consequences, quality of evidence, values and preferences, and resource use and is now recommended by the World Health Organisation. It does present complexities, particularly given that the PICO (patient, intervention, comparator, outcome) questions should be written in binary form. Given the various domains of PsA, and the growing multiplicity of treatments, creating pairwise situations creates myriad scenarios.

2. Lack of evidence

In some cases, PsA-specific trial data were missing and both groups relied on secondary study outcomes and extrapolated data from related conditions. The most obvious example is axial PsA where very few studies are available and evidence from axial spondyloarthritis was used.

3. Conflicting evidence

Where good quality data are lacking, such as methotrexate, observational data report widespread use of MTX in PsA with reasonable response, in contrast to the negative findings in the MIPA RCT[9] that had methodological flaws[10]. In the GRAPPA recommendations, MTX is included as one of the potential DMARDs (alongside sulfasalazine and leflunomide) but given the lack of conclusive evidence these were not ranked. In the EULAR recommendations, MTX is clearly listed as the first line

DMARD therapy despite this controversial evidence base, due to positive expert experience and the limitations of the studies.

4. Heterogeneity of outcome measurement

It is difficult to synthesise the evidence from different studies because of the heterogeneity in outcome measures (e.g. enthesitis or dactylitis).

Conclusions

Based on the experience of both groups, the challenges to optimal development of future PsA recommendations are evident. Both groups involved rheumatologists, patient research partners and at least one dermatologist to provide a multidimensional approach. Both groups based their recommendations on a SLR and included recent data from abstracts to remain current. The groups used different methods to analyse the evidence and achieved consensus using contrasting methods, resulting in unique management algorithms with significant overlap.

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Table 1 - Challenges for management recommendations in PsA

Scope, remit and presentation	Heterogenity of PsA	In a heterogeneous condition such as PsA with multiple domains should recommendations address these aspects of disease individually or attempt to create a single management strategy?
	Stakeholder involvement	Who should be involved in the development process? How to involve patients?
Scope of the systematic literature review	Updating/perennity	In a fast moving research field, how frequently must recommendations be updated?
	Abstract data interpretation	How should data from abstracts be included recognising that these have not been subject to a peer review process?
Assessing the evidence	Assessment of evidence quality	What system for evidence review should be used given the complexity of the condition and limited quality of evidence in some areas?
	Lack of evidence	Is extrapolation from related conditions reasonable in certain domains of PsA, particularly axial PsA where very limited data exist?
	Conflicting evidence	How should conflicting data be balanced?

	Heterogeneity in outcome measures used	How can therapies be compared if different outcome measures are used in different trials?