

Title: New GRAPPA recommendations for the management of psoriasis and psoriatic arthritis: process, challenges and implementation.

Laura C Coates, Ruth Murphy, Philip Helliwell

Laura C Coates, MBChB, PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds UK.

Ruth Murphy MMed Sci (Med Ed), PhD, FRCP, Department of Dermatology Sheffield Teaching Hospitals and Sheffield Children's Hospital

Philip Helliwell, FRCP, Senior Lecturer in Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, and Bradford Teaching Hospitals NHS Foundation Trust, UK.

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R Murphy: None

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CORRESPONDING AUTHOR

Philip Helliwell

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds UK.

Email – p.helliwell@leeds.ac.uk

Telephone - +44113 3923064

Running title

GRAPPA recommendations for management of psoriasis and PsA

Introduction

In 2015, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) presented updated recommendations on the management of psoriasis and psoriatic arthritis (PsA)¹. This updated earlier recommendations² to keep pace with the significant progress in PsA. This editorial summarises the methodology in their development and assesses their practicalities of application in clinical practice both in dermatology and rheumatology.

GRAPPA is a global research group dedicated to both psoriasis and PsA (see www.grappanetwork.org). These recommendations therefore cover treatment of both dermatological and musculoskeletal manifestations. The recommendations were led overall by a small steering committee but appraisal of the evidence and initial generation of treatment recommendations was done in domain subcommittees with expertise in that particular area of PsA. Rheumatologists chaired the groups looking at musculoskeletal manifestation (peripheral joints, axial, enthesitis and dactylitis while dermatologists chaired groups focused on skin and nail disease in the setting of PsA. A new group was also convened to address comorbidities in PsA, including both extra-articular SpA manifestations and distinct comorbidities such as cardiovascular disease, metabolic syndrome, depression and skin cancer³. Patient research partners were included in the groups to ensure a full patient perspective. Following on from the initial development, the GRAPPA patient research partners are now writing a lay summary of the recommendations specifically for dissemination to patients.

The recommendations are based on a large systematic literature review (SLR) to provide the evidence base. In this latest set of recommendations, GRAPPA elected to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) in the latest update⁴ to assess the evidence. GRADE gives strong or

conditional recommendations following assessment of desirable and undesirable consequences, quality of evidence, values and preferences, and resource use. This is now recommended by a number of organisations including the World Health Organisation. After some debate, data from conference abstracts was included in this review even if the full paper had not been published. Recommendations based on high quality abstract data are included to prevent rapid outdateding of the recommendations but these are “conditional” and are clearly demarcated as such in the treatment schema¹.

Face to face meetings of the subcommittees and at GRAPPA full membership meetings took place to allow all active members a voice in the discussion. Drafts of the overarching principles, evidence table and treatment schema were disseminated to all GRAPPA members, including patient research partners to allow feedback from all members before 145 participants voted on agreement. The principle outputs of the GRAPPA recommendations are a summary table of the evidence base for therapies in different domains of psoriatic disease, a table highlighting issues with individual therapies in key comorbidities and a summary treatment schema which includes 6 individual algorithms for the domains of disease which can be used to guide therapeutic decisions (Figure 1). The major differences between the current GRAPPA recommendations, and those recommended by GRAPPA in 2006, are the abandonment of the severity grading (as this was thought not to be evidence based), the inclusion of algorithms for each domain, the separation of the cutaneous domain into skin and nails, and the addition of a section on co-morbidities.

In the U.K, the treatment of patients with psoriasis and psoriatic arthritis is largely directed by the NICE guidelines (<https://www.nice.org.uk/guidance/cg153>). The new GRAPPA recommendations, update this since they include ustekinumab, secukinumab, and PDE4 inhibitors. They also include drugs not currently licensed for treating psoriasis in the U.K, such as the fumaric acid esters. Despite the lack of

trial evidence for methotrexate this drug is still the first DMARD to which rheumatologists turn: it's efficacy on skin is undoubted and observational studies support its use in the joints. However, toxicity remains a problem and the other conventional DMARDs have equally poor evidence for efficacy. Leflunomide is helpful for the joints, but not the skin, and the opposite is true for ciclosporin: both have toxicity issues.

From a rheumatology perspective updating the treatment recommendations are important for several reasons. There have been new developments in pathophysiology, disease assessment, new targeted therapies and the increasing recognition of the co-morbidities. The new disease specific therapies target the IL-12/23 axis with IL-17 'downstream' of IL-23. In addition a new targeted synthetic drug, blocking PDE4, has become available. These emerging therapies have been incorporated into the new schema, but often with a provisional rating, reflecting the fact that the evidence is as yet not fully published. Where these new therapies fit into our current treatment algorithms is as yet undefined. Will the new recommendations change the way we treat psoriatic arthritis in the UK? Initially this is doubtful, as we are dependent on evaluation and approval by NICE. The PDE-4 inhibitor, apremilast, has already undergone a NICE technology appraisal and has been found to not meet cost-benefit criteria (<https://www.nice.org.uk/guidance/ta368>; <https://www.nice.org.uk/guidance/ta372>). In addition, the differential approval of some of these new drugs for psoriasis and psoriatic arthritis will provide challenges and opportunities, and further underscores the importance of collaborative working between dermatology and rheumatology. It is likely that, after methotrexate and sulfasalazine, TNF inhibitors will still be the first biologic of choice but this situation may change with the emergence of new biologics. However, as mentioned above, much will depend on the predominance of skin or musculoskeletal involvement. Ustekinumab may have advantages for the skin but may be less efficacious (than

TNF inhibitors) for the joints. Drugs targeting the IL-17 pathway may be equally efficacious for skin and joints.

In the U.K, dermatologists routinely assess the severity of the psoriasis and the impact the disease has on the patient. In those individuals requiring biological therapy, a clear level of disease severity and impact needs to be demonstrated to justify treatment. However, for the majority with mild to moderate disease, the therapeutic pathway is less clear and less evidence is available. Increasingly the impact the psoriasis is having on the patient is directing the use of standard systemic therapies implementing use at a slightly earlier stage than previously. We would therefore agree that the evidence for the specific recommendations for the treatment of less severe psoriasis is lacking and that the severity grading for the treatment of less severe forms of the disease should be abandoned. The separation of nail disease from skin disease also mirrors current U.K practice as the two sites may show a variable therapeutic response.

The GRAPPA guidelines advocate a patient centred approach and since up to 30% of patients with psoriasis develop psoriatic arthritis therapeutic decisions often cannot be made by simply choosing which affected site is the predominant. For example, if a patient were to present to dermatology with minimal psoriasis, but by screening was found to have psoriatic arthritis, therapy would be escalated from topical to systemic treatment in an attempt to prevent joint damage. Similarly, a patient with well controlled PsA, but poorly controlled genital psoriasis with a high dermatology life quality index, might require switching from one systemic agent to another to optimise the control of the skin as well as preventing permanent joint damage.

Dermatologists and rheumatologists therefore need to work together to develop these patient centred therapeutic pathways. The GRAPPA recommendations are not fully able to address these issues since they are based on the currently published

literature where the outcome measures from RCTs often focus on either the skin or the joints and seldom both.

GRAPPA incorporates the concept that psoriasis and PsA are part of the same (psoriatic) disease, not only of skin and peripheral joints, but encompasses axial disease, enthesitis, dactylitis, nails and other extra-articular associations such as inflammatory bowel disease and cardiovascular morbidity. In the GRAPPA recommendations the treatment approach is tailored according to which disease domain is affected and by keeping the patient at the centre of decision making processes, takes into account their preferences and patient-reported outcome measures. It is important though to adequately screen for psoriasis in hidden sites and for dermatologists to use screening methods to detect joint disease early so that therapy can be optimised.

A further new theme, well established in rheumatoid arthritis, is the concept of treat to target. Recent evidence supports the use of treating to minimal disease activity in psoriatic arthritis ⁵. Treat to target is a shared decision between patient and physician and may involve more than one speciality in the care of the patient. However, recent evidence suggests that most UK rheumatologists are unaware of the available targets in psoriatic arthritis ⁶. Similarly, studies on patients with psoriasis are increasingly using PASI 90 or minimal disease as an outcome measure rather than a PASI 75 response since patients prefer to be clear of their disease.

A further aspect of the GRAPPA recommendations that may impact on health care is the emphasis on co-morbidities. GRAPPA include a useful table where the co-morbidities are listed in rows, and the available treatments in columns (Table 1). The table not only emphasises the range of co-morbidities, but also the interaction between disease therapies and the co-morbidities. These may be helpful (eg monoclonal antibody TNF inhibitor in inflammatory bowel disease) or harmful (eg methotrexate in liver disease). Exactly who should monitor, and manage, the co-

morbidities remains undecided. In the UK some of these are targets for primary care physicians who are reimbursed for assessing and treating cardiovascular risk, hypertension, diabetes, obesity, and depression. We have no doubt that overall outcome for patients will not only be influenced by treatment of the primary disease, but also by recognising and addressing these other comorbidities.

The research agenda is important in highlighting the unmet needs in developing specific outcome measures, using biomarkers to identifying the right drug first time for an individual patient, earlier identification of patients with PsA, and understanding the implementation of treat-to-target in the longer term.

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Table 1 - Considerations for treatment of patients with psoriatic arthritis and concomitant comorbidities (reproduced from Coates et al Arthritis Rheumatol. 2016 Jan 8. doi: 10.1002/art.39573. [Epub ahead of print])

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Cardiovascular Disease	C	?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	?	NI
Congestive Heart Failure	C	C	NI	NI	NI	NI	NI	C	C	C	C	C	?	NI
Obesity	NI	NI	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Metabolic Syndrome	NI	C	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Diabetes	NI	C	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Ulcerative Colitis	?	NI	NI	A	NI	NI	OL	NI	A	A	NI	A	NI	NI
Crohn's Disease	?	NI	NI	A	OL	NI	NI	NI	A	A	A	NI	NI	NI

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Uveitis	NI	P#	NI	NI	NI	NI	NI	?	P	P	NI	NI	NI	NI
Osteoporosis	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Malignancy	NI	NI	NI	NI	NI	NI	NI	C	C	C	C	C	?	NI
Fatty Liver Disease	C	NI	NI	C	C	C	NI	NI	NI	NI	NI	NI	NI	NI
Chronic Kidney Disease	C	NI	NI	NI	C	?	SM	NI	NI	NI	NI	NI	NI	NI
Depression	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	?
Chronic Hepatitis B *	C	NI	NI	NI	C	C	NI	SM	SM	SM	SM	SM	?	NI
Chronic Hepatitis C *	C	NI	NI	NI	C	C	NI	?/P	?	?	?	?	?	NI
Human								SM	SM	SM	SM	SM	?	

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Immunodeficiency														
Virus														

A = Approved for primary therapy of the comorbid condition

C = Reason for caution

NI = no information available

OL = Off-label use for the therapy of the comorbid condition

P = Preferred therapy

SM = Requires special monitoring

? = Data insufficient but concerns have been raised

* When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area.

Corticosteroids used as preferred therapy for uveitis are most commonly given as topical and/or

Comorbidity

- Non-steroidal Anti-inflammatory Drugs**
- Glucocorticoids**
- Hydroxychloroquine**
- Sulfasalazine**
- Methotrexate**
- Leflunomide**
- Cyclosporine**
- Etanercept**
- Adalimumab**
- Infliximab**
- Certolizumab**
- Golimumab**
- Ustekinumab**
- Apremilast**

intraocular injections in preference to oral steroids

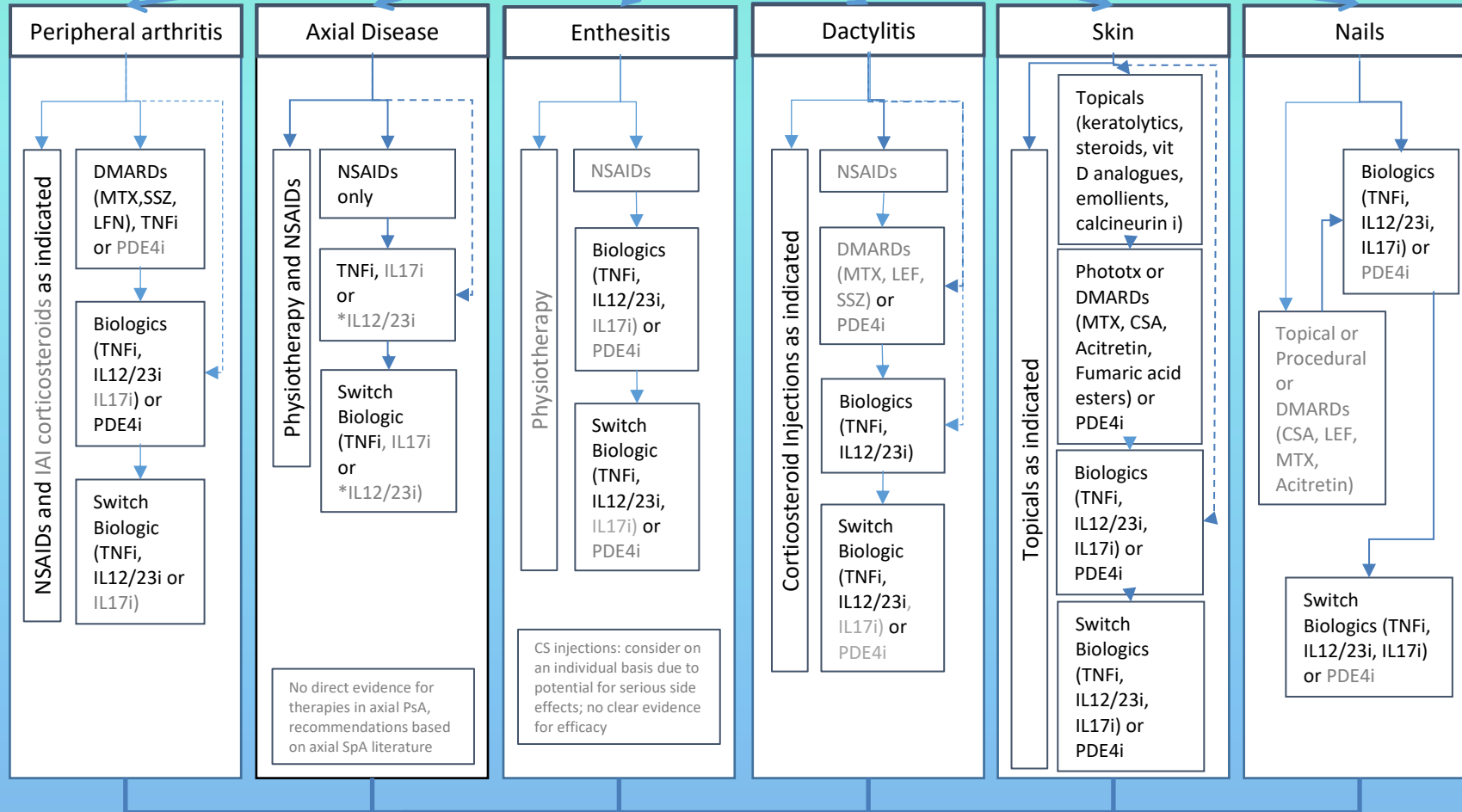
Figure 1: GRAPPA Treatment Schema for Active PsA (reproduced from Coates et al Arthritis Rheumatol. 2016 Jan 8. doi: 10.1002/art.39573. [Epub ahead of print])

Grey text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

DMARDs = disease modifying anti-rheumatic drugs, IL17i = interleukin 17 inhibitors, IL12/23i = interleukin 12/23 inhibitors, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor

Which domains are involved?

Assess activity, impact and prognostic factors



Consider previous therapy, patient choice, other disease involvement and comorbidities. Choice of therapy should address as many domains as possible

Treat, periodically re-evaluate and modify therapy as required

KEY

—> Standard Therapeutic Route

- - -> Expedited Therapeutic Route