OPINION

Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations

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Abstract | Psoriatic arthritis (PsA) is a heterogeneous, potentially severe disease. Many therapeutic agents are now available for PsA, but treatment decisions are not always straightforward. To assist in this decision making, two sets of recommendations for the management of PsA were published in 2016 by international organizations — the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). In both sets of recommendations, the heterogeneity of PsA is recognized and the place of various drugs in the therapeutic armamentarium is discussed. Such agents include conventional DMARDs, such as methotrexate, and targeted therapies including biologic agents, such as ustekinumab, secukinumab and TNF inhibitors, or the targeted synthetic drug apremilast. The proposed sequential use of these drugs, as well as some other aspects of PsA management, differ between the two sets of recommendations. This disparity is partly the result of a difference in the evaluation process; the focus of EULAR was primarily rheumatological, whereas that of GRAPPA was balanced between the rheumatological and dermatological aspects of disease. In this Perspectives article, we address the similarities and differences between these two sets of recommendations and the implications for patient management.

Psoriatic arthritis (PsA) is an irreversible, progressive, heterogeneous inflammatory condition associated with bone damage, joint pain, stiffness, swelling and extra-articular manifestations, such as psoriasis, as well as enthesitis and dactylitis[1,2]. Although the aetiology is still unknown, cells of the innate and adaptive immune system, including type 17 T helper (T_H17) cells, as well as various cytokines, such as interleukins or TNF, have important pathogenetic roles[3]. PsA substantially impairs the quality of life of patients, limits their daily life activities, and affects society at large owing to morbidity-linked productivity losses[4].

PsA is a complex, chronic disease with many treatment options, some of which have been approved since 2010. Not all physicians have much experience in treating patients with PsA, or with the use of novel agents for this disease, and could benefit from up-to-date guidance on the management of PsA. In many countries, and across medical specialties, international management recommendations are considered to be the leading sources of guidance for physicians, inform the development of local recommendations, and provide important information for hospital managers, payors (including insurance companies and public/state social security systems), and regulatory authorities.

In 2016, both the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published recommendations on the management of PsA[5,6], which update their earlier guidelines[7,8]. In both sets of recommendations, treatment algorithms based on a structured process of literature review and expert consensus are proposed[9,10]. Although clinical trials provide data on the efficacy and safety of treatments, this information does not define the position of an individual drug in the therapeutic paradigm; a process that involves careful analysis, balanced interpretation, discussion, and consensus. Unsurprisingly, therefore, the EULAR[5] and GRAPPA[6] recommendations diverge considerably in several areas, despite being derived from the same clinical trial data and having some similarities (TABLE 1).

In this article, we review the EULAR[5] and GRAPPA[6] recommendations for the management of PsA, address their similarities and differences, and provide some guidance as to how clinicians should interpret and apply these statements in practice. We also consider the background and development of the recommendations and their ultimate conclusions and presentation.

The methodologies

Similarities

Literature review and consensus. The task forces from both EULAR and GRAPPA developed research questions, performed extensive literature reviews, and followed predefined consensus processes to develop their respective recommendations[9]. Thus, systematic literature reviews of randomized controlled trials (RCTs) in PsA were performed by both groups to ensure that the recommendations were evidence-based wherever possible.

Task force composition. EULAR and GRAPPA each recognized the need for a variety of perspectives within the committee or task force. To this end, both rheumatologists and patients contributed to the development of the recommendations[11], allowing the views of stakeholders to be integrated[12]. In both publications, potential conflicts of interest are stated for each task force member. In addition, all members of the EULAR task force were required to

Table 1 | **Summary of the 2015 EULAR and GRAPPA recommendations for PsA**

Feature	EULAR[5]	GRAPPA[6]
Composition of the recommendations committee	Physicians and patients involved in the development process	
	Rheumatologists and dermatologists involved the development process	
	Additional representation of allied health professionals	Greater representation by dermatologists
General principles	Treatment target defined as remission or, alternatively, low or minimal disease activity	Treating to target recommended, but no specific target defined
	Overarching principle states that comorbidities should be considered	Specific literature review addressing prevalence of comorbidities, the need for screening, and potential effect on choice of therapy
Predominant axial or entheseal disease	bDMARDs without prior use of a csDMARD	
Drugs		
Methotrexate	Recommended as the csDMARD of choice	Considered alongside other csDMARDs with no specific preference
TNF inhibitors	Recommended for use after failure of csDMARDs for predominant peripheral disease or earlier in predominant axial or entheseal disease	
	• Recommended for use after failure of csDMARDs • Clear preference for TNF inhibitors as the first-line bDMARD	• Potential to use as a first-line therapy, before csDMARDs, in patients with severe active disease • No clear preference given to TNF inhibitors as the first-line bDMARD
Secukinumab and ustekinumab	Recommended for use after failure of methotrexate, but TNF inhibitors are preferred as the first-line bDMARD	Recommended alongside TNF inhibitors
Apremilast	Recommended for use after methotrexate if bDMARDs are contraindicated	• Recommended for use after failure of csDMARDs or if csDMARDs are contraindicated • Conditionally recommended before csDMARDs in certain cases

bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PsA, psoriatic arthritis.

declare conflicts of interest to the Executive Committee before the process of guideline development commenced.

Use of nomenclature. The nomenclature used for PsA treatments was similar in the EULAR and GRAPPA publications. Drugs such as methotrexate and sulfasalazine were grouped under the term 'disease-modifying antirheumatic drug' (DMARD). In the EULAR recommendations[5], additional subclasses of DMARDs were specified, as defined in other publications[13].

Notably, disease-modifying properties for these agents might not have been demonstrated formally in PsA. However, changes in disease pathways have been shown in the setting of rheumatoid arthritis (RA) and the process of joint destruction via activation of osteoclasts is similar in RA and PsA (with additional osteoproliferative changes in PsA)[14].

Differences

Task force composition. An examination of the primary missions of EULAR and GRAPPA and composition of the respective task forces provides background context to the recommendations. The focus of EULAR is rheumatic diseases and it is an organization of European rheumatological professional and patient societies. The physicians within the task force were almost exclusively rheumatologists, with the exception of one dermatologist[5]. By contrast, GRAPPA is concerned specifically with psoriasis and PsA, and has individual members and is not a member of any umbrella organization. Many members of GRAPPA are dermatologists, and this specialty was well represented on the GRAPPA task force. Consequently, dermatological aspects of treatment were specifically considered[6]. On the basis of these differences in organizational emphasis, the EULAR recommendations[5] focused on the musculoskeletal manifestations of PsA, including synovitis, enthesitis, dactylitis, and axial involvement; whereas the GRAPPA publication[6] addressed all aspects of the psoriatic disease spectrum including clinically relevant skin or nail disease.

Part of the rationale for the inclusive approach used by GRAPPA is the recognition that skin and nail involvement in PsA can substantially impair quality of life. Potentially, the rheumatologist might be the sole provider of care for the patient; therefore, awareness of the management choices for skin disease in PsA might be helpful and also influence the treatment choice for arthritis. By contrast, the approach followed by EULAR was to focus on the musculoskeletal impact of PsA, in the knowledge that many rheumatological therapies also improve inflammatory skin disorders, including psoriasis. EULAR recommends in its overarching principles that musculoskeletal conditions in patients with psoriasis should be treated by rheumatologists, on the basis of the wide differential diagnosis and disease heterogeneity, but also that a dermatologist should be consulted in cases of severe skin disease[5].

International representation. Both EULAR and GRAPPA are international, and both publications[5,6] are international in remit. However, the EULAR task force was predominantly composed of European participants, whereas membership of the GRAPPA committee had approximately equal representation from Europe and North America. How this difference in geographical representation might have influenced the recommendations is not clear.

Assessment of clinical trial data. The EULAR task force used the Oxford Centre for Evidence-based Medicine (OCEBM) – Levels of Evidence criteria (published in 2009) to assess the clinical trial data, whereas the committee from GRAPPA used the 2016 Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[15] (TABLE 2). GRADE allows treatment recommendations to be either 'strong' (the therapy would be offered to most patients with the condition) or 'conditional' (only some patients would be likely to be prescribed the therapy)[15]. By contrast, EULAR defined the patient groups most likely to benefit from a given therapy on the basis of clinical criteria such as the absence or presence of poor prognostic

Table 2 | **Comparison of GRADE and OCEBM levels of evidence**

Method used to assess data	Strengths	Weaknesses
GRADE[15] (used by GRAPPA)	• 'Strong' or 'conditional' recommendations can be made following assessment of desirable and undesirable consequences, quality of evidence, values and preferences, and resource use • This approach is recommended by several organizations, including the WHO[59]	• Users are presented with a number of complexities, particularly given that the PICO questions should be written in binary form. Given the various domains of PsA, and the growing multiplicity of treatments, creating pairwise situations to fit traditional PICO questions in a GRADE approach creates myriad scenarios • Physicians might find using 'conditional' recommendations challenging
OCEBM Levels of Evidence (used by EULAR)	• Recommendations can be made solely on the basis of expert opinion when other evidence is lacking • The level of available evidence and quality of the data are clearly reflected through the strength of the recommendation	• Readers might overlook the fact that some recommendations are based on weak evidence or expert opinion only, despite levels of evidence being stated

EULAR, European League Against Rheumatism; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; OCEBM, Oxford Centre for Evidence-based Medicine; PICO, patient, intervention, comparator, outcome.

factors. Each EULAR recommendation was also attributed a level of evidence and strength of recommendation according to OCEBM criteria.

Another difference between the two sets of recommendations concerns the assessment of data presented only as congress abstracts. Both groups included such data in their literature reviews. EULAR assessed these abstracts in a similar way to manuscripts published in peer-reviewed journals (provided that the data could be extracted) on the assumption that the final publication would be in line with the abstract data, as is usually the case, in particular with RCTs. GRAPPA, however, only allowed conditional recommendations to be made on the sole basis of presented abstracts, as the data had not been subject to peer review and the information available was limited.

The recommendations

Similarities

As we have shown, the methodologies used to in the development of the EULAR[5] and GRAPPA[6] publications differed, as did the composition of the task forces. Notably, however, the recommendations made by the two groups were in agreement for many aspects of the management of PsA, as outlined below.

Overarching principles. EULAR had already included overarching principles in the earlier recommendations statement published in 2012 (REF. 7); the 2016 GRAPPA recommendations[6] added overarching principles, which were not part of the 2009 recommendations[8]. These principles encompass basic precepts in the management of PsA that, although generic, deserve emphasis. The content of the overarching principles is similar between the two publications and relates to the heterogeneity of PsA, collaboration among practitioners in management, and shared decision-making with patients.

Clinical presentation to guide treatment. Both sets of recommendations recognize that PsA is a heterogeneous disease and that some patients have predominant manifestations that should guide treatment choices. The EULAR publication[5] has a single flow chart that focuses on peripheral arthritis. This scheme also addresses other manifestations of PsA, particularly predominant axial disease, enthesitis, or dactylitis (requiring a different initial, but subsequently similar, treatment approach to peripheral arthritis) and predominant skin disease (requiring the patient to be referred to a dermatologist). The GRAPPA recommendations[6] provide six separate flow charts, one for each treatment domain (peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail involvement) presented side by side, with the aim that therapies should target as many active domains as possible. Therefore, although the presentation of information differs, both sets of recommendations underscore the various disease domains and how they should be addressed therapeutically.

Step-up approaches. The principal feature of both sets of recommendations is a treatment flowchart or scheme, suggesting how various therapies might be used in patients with PsA[5,6]. These charts follow a 'step-up' approach to therapy, although this principle is clearer in the EULAR recommendations than in the GRAPPA publication (FIGS 1–3). Unfortunately, data in the literature on treatment strategies in PsA are scarce. Therefore, a step-up regime seems appropriate to balance safety with efficacy.

The first step involves treatment of the symptoms of PsA; for example, by use of NSAIDs and, where applicable, local glucocorticoid injections. NSAIDs have been shown to be efficacious for the relief of joint symptoms, particularly in patients with mild joint disease, in clinical trials[16]. However, the effect of NSAIDs on skin lesions has not been demonstrated, and the risks and contraindications of this treatment need to be considered[16]. Local glucocorticoid injections alleviate pain and inflammation in joints, tendon sheaths, and entheses[17]. If ineffective, this step might be followed by escalation to the use of conventional synthetic DMARDs (csDMARDs), with the exception of patients with symptomatic enthesitis or axial disease, in whom these drugs are not effective. Both sets of recommendations propose that these individuals, as well as those with peripheral disease in whom csDMARDs are insufficient, should receive biologic agents, targeted synthetic DMARDs (tsDMARDs), or both (FIGS 1–3). The clinical response to therapy and the concerns of the patient should be evaluated periodically in accordance with a treat-to-target approach.

Predominant axial or entheseal disease. In both the EULAR[5] and GRAPPA[6] publications, the early use of biologics is recommended in patients for whom csDMARDs are not efficacious, such as those with predominant axial or entheseal manifestations of PsA. In fact, the proposed order of drug use is very similar for each of the two types of disease (FIGS 2,3). In both sets of recommendations, the paucity of data specific to axial PsA is highlighted, and the committees suggest extrapolation from evidence and recommendations pertaining to axial spondyloarthritis to guide therapy in patients with predominant axial disease[18].

Differences

Distinguishing clinical presentations. The EULAR committee developed a single figure to summarize the management of PsA[5], whereas the GRAPPA publication[6] includes six separate flow charts, one for each manifestation of the disease and each based on an individual literature search. Of note, EULAR, in contrast to GRAPPA, did not develop recommendations for skin disease and did not address nail disease specifically. As mentioned above, this intentional omission reflects the remit of EULAR (centred on rheumatologists) versus that of GRAPPA (with a combined rheumatology and dermatology constituency and a greater focus on skin disease).

Treatment algorithms. The EULAR treatment algorithm is divided into phases with a chronological (or sequential) approach and, therefore, proposes the order in which drugs should be prescribed[5] (FIGS 1–3). In the GRAPPA algorithm[6], groups of drugs are recommended in chronological order (for example, csDMARDs to be prescribed first), but within each group the drugs are not always presented in sequential order. Therefore, the flow charts in the GRAPPA publication allow more room for interpretation in approaches to treatment, depending on the severity of presentation, patient choice, cost considerations, and comorbidities (FIGS 1–3). This format was developed by the GRAPPA committee partly because little head-to-head evidence is available to guide the selection of one agent in a class over another. In the absence of a clear evidence base to direct first-line therapy, access to several drugs gives physicians scope to personalize management decisions to the individual patient. By contrast, the approach proposed by EULAR fulfils one of the main goals of treatment recommendations by providing specific guidance for rheumatologists who are unsure of which drugs to use in which order. Given the increasing body of evidence in PsA, clinicians (particularly those who are not research-oriented) might welcome such information.

Prognostic factors. In the EULAR recommendations[5], the algorithm takes into account disease severity and its predictors and proposes several ordered treatment schemes based, in part, on prognosis. The poor prognostic factors defined by EULAR are: five or more actively involved joints that are tender or swollen; radiographic damage (joint destruction), particularly if inflammation is present; elevated levels of acute-phase reactants (that is, any value above the upper limit of normal as serological indication of inflammation); and extra-articular manifestations of PsA, particularly dactylitis[16–22]. By contrast, although these evidence-based predictors of poor prognosis are also listed in the GRAPPA recommendations[6] and should be taken into account when planning treatment, such prognostic factors are not specifically reflected within the treatment schema. In addition, the GRAPPA flow charts for therapy include routes reflecting standard clinical practice (for example, a step-up approach with csDMARDs being used before biologic agents in patients with peripheral arthritis) and expedited therapy (for example, the early use of biologic agents in patients with peripheral arthritis) (FIG. 1), and the clinician is given increased flexibility on the choice of 'route' and of therapies within a 'route' used for an individual patient depending on prognostic factors, comorbidities, availability of therapy and patient preference.

Treating to target. The EULAR recommendations focus on a treat-to-target strategy[23]. The targets to be achieved within 3–6 months of starting therapy are defined as 'remission' or, alternatively, 'low or

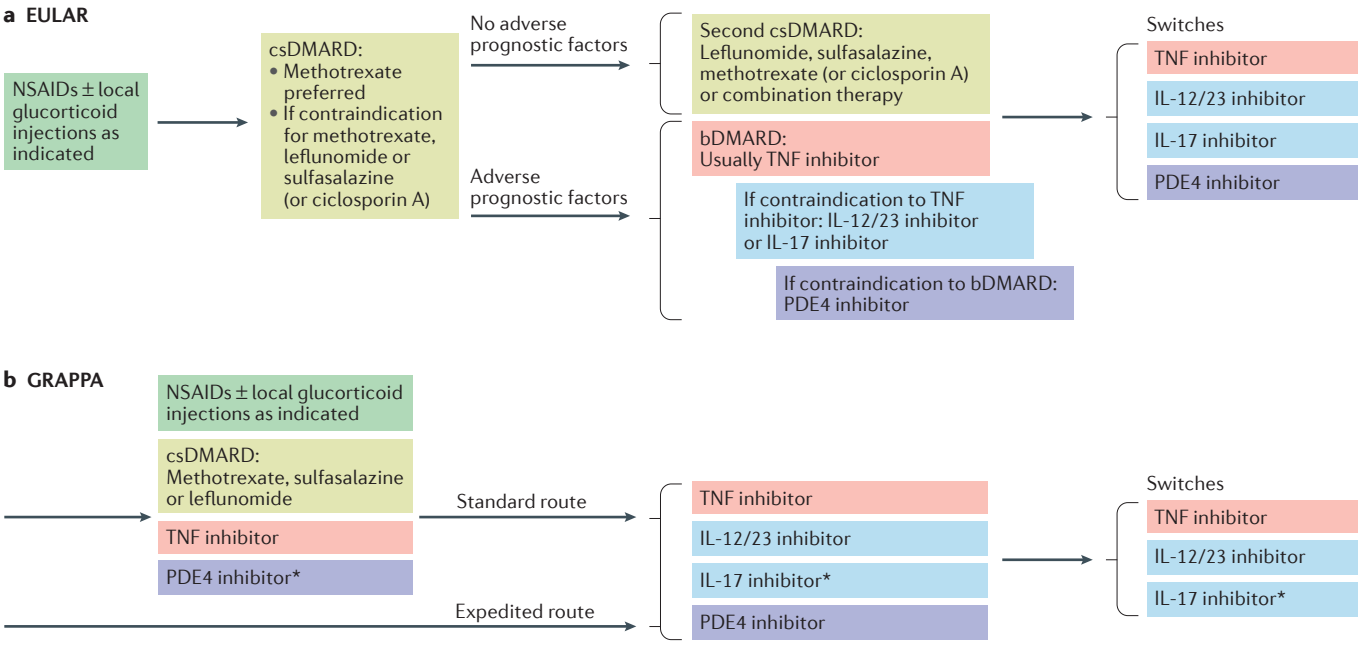

Figure 1 | **Simplified EULAR and GRAPPA treatment algorithms for predominant peripheral psoriatic arthritis[5,6].** The order of drug use proposed for patients with psoriatic arthritis (PsA) and predominant peripheral joint involvement, with a step-up approach (indicated by staggered boxes) in case of inefficacy or toxicity. *Conditional recommendation in the GRAPPA) guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasisand Psoriatic Arthritis; PDE4, phosphodiesterase 4.

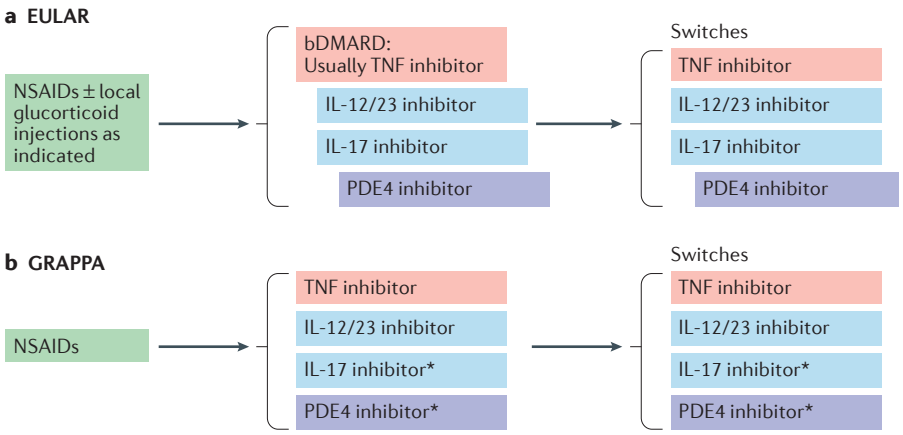

Figure 2 | **Simplified EULAR and GRAPPA treatment algorithms for predominant entheseal psoriatic arthritis[5,6].** The order of drug use proposed for patients with psoriatic arthritis (PsA) and predominant entheseal involvement, with a step-up approach (indicated by staggered boxes) in case of inefficacy or toxicity. *Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic DMARD; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PDE4, phosphodiesterase 4.

minimal disease activity'. Patients should be assessed regularly and, if the target is not attained, treatment should be escalated to the next phase of the algorithm. The GRAPPA committee reviewed evidence on treatment strategies and 'treat-to-target' is referred to in the overarching principles; however, specific recommendations to this effect were not made[24,25]. Therefore, although the principle of minimizing disease activity and treating to target is supported by both sets of recommendations, the EULAR paper includes a specific recommendation that this strategy should be followed, whereas the GRAPPA publication does not. The difference in emphasis on a strategy of treating to target between the two documents reflects the lack of consensus on definitions of 'remission' and acceptable residual disease activity levels in PsA, as well as their predictors and effects on long-term outcomes[26,27]. Members of GRAPPA held the opinion that the paucity of evidence on appropriate outcome measures in PsA precluded specific recommendations being made in this important area.

Minimal disease activity (MDA) in PsA has been defined as the presence of five out of seven criteria, comprising musculoskeletal and skin manifestations and patient-reported outcomes[28–31]. The results of the Tight Control in PsA (TICOPA) trial[24], published in 2015, provide new evidence for treating to target using the MDA criteria. In this trial, patients with active PsA were randomly allocated to either standard care or 'tight control' with treatment escalation (csDMARDs progressing to biologic agents) if the predefined target of MDA was not reached. Patients in the tight-control group had more favourable clinical and patient-reported outcomes after 48 weeks than those who received standard care[24]. The TICOPA trial[24] provided the first evidence for the validity of a treat-to-target approach in PsA, suggesting that MDA could be a useful treatment target in PsA.

Treatment targets remain on the research agenda for PsA. In 2016, definitions of 'remission' and 'low disease activity' were developed using the Disease Activity Index for Psoriatic Arthritis (DAPSA), which is a simple sum of five variables related to psoriatic joint disease[32]. DAPSA has proven face validity and construct validity[33], and remission status is associated with no or minimal residual ultrasound signals in the joints[34]. Modification of the MDA criteria to require all seven criteria to be met have recently been proposed as defining 'very low' disease activity although this state remains to be validated[35]. Other measures with validated definitions of remission include the Composite Psoriatic Disease Activity Index (CPDAI) and the GRAPPA-developed PsA Disease Activity Score (PASDAS) and GRAPPA Composite Exercise (GRACE) Index. These indices are more time-consuming to use than DAPSA, but they encompass assessment of several PsA domains, including dactylitis and enthesitis, to give a total score. Certain drugs can improve some disease domains (for example, the skin) more than others, and how these differences are reflected in the multidimensional composite measures is not known. Future studies will determine the usefulness of these outcome measures as treatment targets.

Methotrexate and other csDMARDs. In the EULAR recommendations[5], methotrexate is named as the csDMARD of choice for PsA whereas, in the GRAPPA recommendations[6], the csDMARDs methotrexate, leflunomide and sulfasalazine are discussed as a class without one drug being given preference over another (FIG. 1). Little high-quality data exist to support the use of csDMARDs in PsA[16,36]. Although methotrexate is the most commonly prescribed csDMARD for PsA in most health care systems, the evidence of efficacy for this drug is limited. To date, the Methotrexate in PsA (MIPA) trial[37] is the only sufficiently powered, randomized, placebo-controlled trial of methotrexate in PsA. The primary outcome of the study was not met; however, patients with mild disease activity were included in the trial, which reduced the sensitivity to change in outcomes. Moreover, the target dose of methotrexate was low (15 mg) with slow dose escalation and the primary endpoint was PsA response, which requires an improvement of ≥1 swollen joints, possibly an overly ambitious goal in patients with few swollen joints[38]. Interestingly, supplementary data showed a large response to methotrexate in the subgroup of patients with polyarticular disease[37]. On the basis of these data, both EULAR[5] and GRAPPA[6] recommend methotrexate, but the EULAR task force was more directive in the algorithm. EULAR also took into account data from open-label trials and registries, which show that methotrexate is effective for treatment maintenance[39,40], as well as the efficacy of methotrexate demonstrated in the TICOPA trial[24]. The GRAPPA committee felt that, although some data exists to support the use of methotrexate, this drug could not be considered superior to other csDMARDs on the basis of the available evidence.

Early use of biologic agents. As acknowledged above, although approval for and availability of new therapies in PsA is increasing, little or no data exist to inform treatment order or strategy. In the GRAPPA treatment algorithm, patients with severe or poor prognosis peripheral joint disease can be prescribed biologic agents as a first-line therapy without having been given a csDMARD. This recommendation was made on the basis of

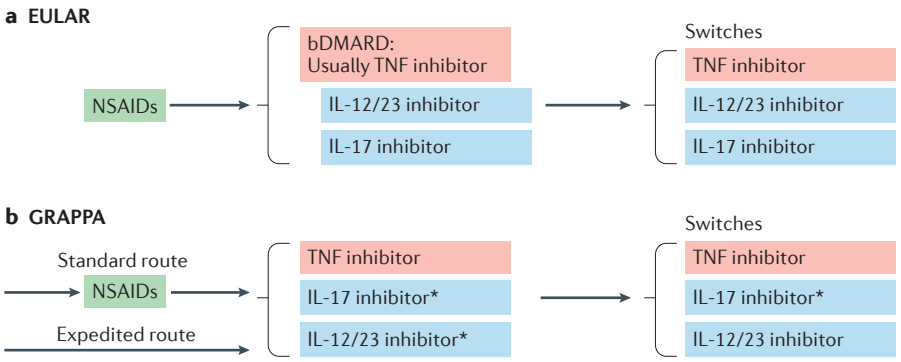

Figure 3 | **Simplified EULAR and GRAPPA treatment algorithms for predominant axial psoriatic arthritis[5,6].** The order of drug use proposed for patients with psoriatic arthritis (PsA) and predominant axial involvement, with a step-up approach (indicated by staggered boxes) in case of inefficacy and/or toxicity. *Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic DMARD; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

evidence that a number of biologic agents are highly effective for patients who have not previously failed csDMARDs[41]. The EULAR recommendations make no such allowances (FIG. 1). The EULAR group deemed that prescribing a biologic before a csDMARD for peripheral disease would be illogical for two main reasons: first, the relatively small expected additional benefits of a biologic agent compared with csDMARDs, as illustrated by the only very slight superiority of infliximab plus methotrexate over methotrexate alone in methotrexate-naive patients in the RESPOND study[42]; and second, the lack of high-level evidence pointing to harm, such as major progression of damage or disability, from delaying therapy with biologic agents (that is, by prescribing methotrexate first). EULAR also considered the cost–benefit ratio of using biologic agents before csDMARDs, in line with the predefined overarching principle that 'efficacy, safety, and costs' should be taken into account when making treatment decisions[5]. The international membership of GRAPPA considered cost to be an important issue that should be addressed on a local level and so did not make general recommendations related to cost–benefit ratios.

TNF inhibitors and other biologic agents. TNF inhibitors have demonstrated efficacy in all aspects of PsA treatment, including inhibition of structural joint damage[16,36,43]. In both the EULAR[5] and GRAPPA[6] documents, recommendations are made relating to a number of biologic agents with various modes of action (in addition to the TNF inhibitors available at the time the previous recommendations were published[7,8]). In both publications[5,6], data on the IL-17A inhibitor secukinumab as well as the IL-12 and IL-23 inhibitor ustekinumab are reviewed, including the effects of these agents on radiographic disease progression[44–47]. TNF inhibitors are given preference as first-line biologic therapy in the EULAR recommendations[5], on the basis of the longer duration of experience with these drugs and the greater quantity of long-term efficacy and safety data available in comparison with newer biologic agents. In the GRAPPA recommendations[6], the assumption is made that TNF inhibitors would remain the first choice of biologic agents for most patients, although TNF inhibitors and other biologics are included in the same 'step' in the GRAPPA flow charts, which enables newer biologic agents to be used as first-line therapy over TNF inhibitors if the clinician deems it appropriate. Furthermore, in the GRAPPA publication, all biologic agents are placed at the same level for some PsA domains. In particular, given the impressive results from trials of IL-17A inhibitors in patients with psoriasis[48,49], dermatologists might consider these agents as a first-line biologic therapy for patients with severe skin disease.

Apremilast. Apremilast is an oral tsDMARD that inhibits phosphodiesterase 4, which has been demonstrated to be efficacious in PsA[43]. The four RCTs of apremilast in PsA performed so far show moderate efficacy for this drug on joints, skin, and entheses[50–53]. No radiographic data are available, as none were collected in these trials. The groups from EULAR and GRAPPA both discussed at length the position of this drug. Given the moderate effect of apremilast on most outcomes in PsA, the unknown effect on structural disease progression, and the relationship between benefit, risk and costs, EULAR recommended that this drug should only be prescribed to patients who do not achieve treatment targets with csDMARDs, and for whom biologic agents are not appropriate[5]. By contrast, apremilast received a 'strong' recommendation by GRAPPA for patients with peripheral arthritis unresponsive to csDMARDs, and a 'conditional' recommendation for patients with peripheral arthritis who were DMARD-naive[6]. These recommendations were based on data from the PALACE-1 and PALACE-4 studies[50,53]. In the GRAPPA recommendations[6], the lack of data on radiographic progression for apremilast is acknowledged, but this drug is considered to be a potential first-line therapy for peripheral PsA given its low toxicity and benign safety profile. Here GRAPPA (with its large North American membership) seems to match the prescribing habits of physicians in the USA, on the basis of first-year post-launch sales of apremilast in North America[54]. The EULAR committee did not arrive at this conclusion, in part because head-to-head trials comparing apremilast and methotrexate have not been performed, and the cost of apremilast precludes its recommendation as a first-line therapy in the absence of trials that formally address this comparison and radiographic data (although radiographic information is also not available for the use of methotrexate in PsA). Clearly, determining the place of new drugs for which no long-term follow-up data exist is a challenge. In this case, the task forces of EULAR and GRAPPA chose to solve the problem differently; EULAR placed emphasis on efficacy, lack of radiographic data, and cost–benefit ratio[5], whereas GRAPPA focused on ease of use and safety[6].

Biosimilars. The success of innovator biological products and expiry of patents have led biopharmaceutical companies to develop biosimilar products over the past 5 years. A biosimilar is a biological product that is highly similar to an existing reference biological product. Biosimilars can be approved by the FDA and European Medicines Agency if they demonstrate their similarity to the reference product[55]. Relevant to PsA, biosimilars of the earlier TNF blockers, including infliximab and

Box 1 | **Controversies in the understanding and management of PsA**

- Are all manifestations of psoriatic disease (such as in the entheses, joints, skin, and spine) driven by the same or different pathophysiological mechanisms?
- Can similar manifestations of PsA be driven by different pathophysiological mechanisms in different patients?
- Is methotrexate truly effective in PsA, and in which group(s) of patients?
- Which csDMARDs provide the most benefit in PsA?
- Do csDMARDs inhibit progression of joint damage?
- Which of the approved bDMARDs are most effective in PsA?
- Can the differential response to the available bDMARDs be predicted?
- At what stage of disease are bDMARDs most effective?
- Does apremilast inhibit progression of joint damage?
- How should differential responses in skin and musculoskeletal manifestations to a given therapy be addressed?
- Should disease activity be assessed using specific scores for each individual, or by a global score comprising several or all manifestations of PsA?
- Is assessment of joint damage in clinical trials important?

bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; PsA, psoriatic arthritis.

etanercept, are currently in development or already approved. Biosimilar anti-TNF agents have been studied in RA and ankylosing spondylitis[56].

In the EULAR recommendations[5], biosimilars are addressed specifically in terms of European Medicines Agency or FDA approval, as the use of these agents has the potential to reduce costs substantially and increase accessibility in the least affluent countries[57]. The use of biosimilars is not specifically addressed in the GRAPPA document[6]; however, all TNF inhibitors are grouped together by GRAPPA and biosimilars approved by regulatory agencies could be considered within this group.

Comorbidities. EULAR places consideration of comorbidities in decision-making as an overarching principle[5], whereas GRAPPA published a specific systematic literature review and formulated recommendations based on assessment of important comorbidities and the implications of comorbidities for treatment options[58]. In the GRAPPA literature review, data were collated on potential interactions between comorbidities and the therapies commonly prescribed for PsA (not limited to randomized trials). Some drugs are particularly useful for the treatment of both PsA and related comorbidities or coexisting conditions. For example, in patients with PsA and inflammatory bowel disease some therapies, such as TNF inhibitors, can be used to effectively treat both conditions. Cautionary comments or special considerations are also stated for the use of some other therapies, such as TNF inhibitors in patients with concomitant heart failure or chronic viral infection[6].

Conclusions and perspectives

The new treatment recommendations from EULAR[5] and GRAPPA[6] provide clinicians with evidence-based advice for the treatment of patients with PsA. Some important differences exist between these two sets of recommendations, in particular the focus on rheumatological manifestations of disease by EULAR compared with the balance between rheumatological and dermatological aspects by GRAPPA. However, the overarching principles of the two publications are similar, as is the underlying step-up approach to therapy. Some overlap in treatment recommendations exists, which is reassuring to physicians when making treatment decisions. In the future, efforts to align recommendations produced by various organizations will improve ease of use for clinicians and patients alike. Fortunately, differences in recommendations for the treatment of PsA have already diminished over time, heralding a trend towards a common approach.

Both the EULAR and GRAPPA recommendations highlight the need for future research in PsA to guide the use of therapies. The current lack of evidence on the treatment of PsA leaves a number of controversies and differences of opinion both between and within recommendation groups (BOX 1). Other important areas for research are the implementation of these recommendations in clinical practice, as well as determining the level of support they provide in making treatment decisions and their effect on patient outcomes. Time will tell the extent to which clinicians and patients will gravitate towards these recommendations, and most importantly, whether this will lead to improved outcomes and quality of life for patients with PsA.

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1. Chandran, V. & Raychaudhuri, S. P. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *J. Autoimmun.* **34**, J314–J321 (2010).
2. Boehncke, W. H. & Menter, A. Burden of disease: psoriasis and psoriatic arthritis. *Am. J. Clin. Dermatol.* **14**, 377–388 (2013).
3. Frleta, M., Siebert, S. & McInnes, I. B. The interleukin-17 pathway in psoriasis and psoriatic arthritis: disease pathogenesis and possibilities of treatment. *Curr. Rheumatol. Rep.* http://dx.doi.org/10.1007/s11926-014-0414-y (2014).
4. Krueger, G. *et al.* The impact of psoriasis on quality of life: results of a 1998 national psoriasis foundation patient-membership survey. *Arch. Dermatol.* **137**, 280–284 (2001).
5. Gossec, L. *et al.* European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann. Rheum. Dis.* **75**, 499–510 (2016).
6. Coates, L. C. *et al.* Group for Research and Assessment of Psoriasis and Psoriatic Arthritis: treatment recommendations for psoriatic arthritis 2015. *Arthritis Rheumatol.* **68**, 1060–1071 (2016).

7. Gossec, L. *et al.* European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann. Rheum. Dis.* **71**, 4–12 (2012).
8. Ritchlin, C. T. *et al.* Treatment recommendations for psoriatic arthritis. *Ann. Rheum. Dis.* **68**, 1387–1394 (2009).
9. van der Heijde, D. *et al.* 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann. Rheum. Dis.* **74**, 8–13 (2015).
10. Coates, L. *et al.* New GRAPPA and EULAR recommendations for the management of psoriatic arthritis: process and challenges faced. *Rheumatology (Oxford)* (In press).
11. de Wit, M. P. *et al.* European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. *Ann. Rheum. Dis.* **70**, 722–726 (2011).
12. Cheung, P. P. *et al.* Recommendations for the involvement of Patient Research Partners (PRP) in OMERACT working groups. A report from the OMERACT 2014 working group on PRP. *J. Rheumatol.* **43**, 187–193 (2016).
13. Smolen, J. S., van der Heijde, D., Machold, K. P., Aletaha, D. & Landewé, R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann. Rheum. Dis.* **73**, 3–5 (2014).
14. Shaw, A. T. & Gravallese, E. M. Mediators of inflammation and bone remodeling in rheumatic disease. *Semin. Cell Dev. Biol.* **49**, 2–10 (2016).
15. Schünemann, H. J. *et al.* GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J. Clin. Epidemiol.* **76**, 89–98 (2016).
16. Ash, Z. *et al.* A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann. Rheum. Dis.* **71**, 319–326 (2012).
17. Eder, L. *et al.* Predictors of response to intra-articular steroid injection in psoriatic arthritis. *Rheumatology (Oxford)* **49**, 1367–1373 (2010).
18. Braun, J. *et al.* 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann. Rheum. Dis.* **70**, 896–904 (2011).
19. Bond, S. J., Farewell, V. T., Schentag, C. T. & Gladman, D. D. Predictors for radiological damage in psoriatic arthritis: results from a single centre. *Ann. Rheum. Dis.* **66**, 370–376 (2007).
20. McHugh, N. J., Balachrishnan, C. & Jones, S. M. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology (Oxford)* **42**, 778–783 (2003).
21. Gladman, D. D. *et al.* Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. *Arthritis Res. Ther.* **12**, R113 (2010).
22. Cresswell, L., Chandran, V., Farewell, V. T. & Gladman, D. D. Inflammation in an individual joint predicts damage to that joint in psoriatic arthritis. *Ann. Rheum. Dis.* **70**, 305–308 (2011).
23. Smolen, J. S. *et al.* Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann. Rheum. Dis.* **73**, 6–16 (2014).
24. Coates, L. C. *et al.* Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* **386**, 2489–2498 (2015).
25. Acosta Felquer, M. L. *et al.* Remission criteria and activity indices in psoriatic arthritis. *Clin. Rheumatol.* **33**, 1323–1330 (2014).
26. Van den Bosch, F., Kavanaugh, A., Kron, M., Kupper, H. & Mease, P. J. Clinical remission in patients with active psoriatic arthritis treated with adalimumab and correlations in joint and skin manifestations. *J. Rheumatol.* **42**, 952–959 (2015).
27. Cantini, F., Niccoli, L., Cassarè, E., Kaloudi, O. & Nannini, C. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. *Biologics* **6**, 201–206 (2012).
28. Coates, L. C. & Helliwell, P. S. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res.* **62**, 965–969 (2010).
29. Coates, L. C., Cook, R., Lee, K.-A., Chandran, V. & Gladman, D. D. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. *Arthritis Care Res.* **62**, 970–976 (2010).
30. Coates, L. C., Fransen, J. & Helliwell, P. S. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann. Rheum. Dis.* **69**, 48–53 (2010).
31. Haddad, A. *et al.* Minimal disease activity and anti-tumor necrosis factor therapy in psoriatic arthritis. *Arthritis Care Res.* **67**, 842–847 (2015).
32. Schoels, M., Aletaha, D., Alasti, F. & Smolen, J. S. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann. Rheum. Dis.* **75**, 811–818 (2016).
33. Salaffi, F., Ciapetti, A., Carotti, M., Gasparini, S. & Gutierrez, M. Disease activity in psoriatic arthritis: comparison of the discriminative capacity and construct validity of six composite indices in a real world. *Biomed. Res. Int.* **2014**, 528105 (2014).
34. Husic, R. *et al.* Disparity between ultrasound and clinical findings in psoriatic arthritis. *Ann. Rheum. Dis.* **73**, 1529–1536 (2014).
35. Coates, L. C. & Helliwell, P. S. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J. Rheumatol.* **43**, 371–375 (2016).
36. Coates, L. C., Kavanaugh, A., Ritchlin, C. T. & GRAPPA Treatment Guideline Committee. Systematic review of treatments for psoriatic arthritis: 2014 update for the GRAPPA. *J. Rheumatol.* **41**, 2273–2276 (2014).
37. Kingsley, G. H. *et al.* A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)* **51**, 1368–1377 (2012).
38. Pincus, T., Bergman, M. J. & Yazici, Y. Limitations of clinical trials in chronic diseases: is the efficacy of methotrexate (MTX) underestimated in polyarticular psoriatic arthritis on the basis of limitations of clinical trials more than on limitations of MTX, as was seen in rheumatoid arthritis? *Clin. Exp. Rheumatol.* **33** (Suppl. 93), S82–S93 (2015).
39. Lie, E. *et al.* Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **69**, 671–676 (2010).
40. Coates, L. C. & Helliwell, P. S. Methotrexate efficacy in the Tight Control in Psoriatic Arthritis study. *J. Rheumatol.* **43**, 356–361 (2016).
41. Acosta Felquer, M. L. *et al.* Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. *J. Rheumatol.* **41**, 2277–2285 (2014).
42. Baranauskaite, A. *et al.* Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann. Rheum. Dis.* **71**, 541–548 (2012).
43. Ramiro, S. *et al.* Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann. Rheum. Dis.* **75**, 490–498 (2016).
44. McInnes, I. B. *et al.* Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* **382**, 780–789 (2013).
45. Ritchlin, C. *et al.* Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann. Rheum. Dis.* **73**, 990–999 (2014).
46. Mease, P. J. *et al.* Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N. Engl. J. Med.* **373**, 1329–1339 (2015).
47. McInnes, I. B. *et al.* Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **386**, 1137–1146 (2015).
48. Griffiths, C. E. *et al.* Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* **386**, 541–551 (2015).
49. Langley, R. G. *et al.* Secukinumab in plaque psoriasis — results of two phase 3 trials. *N. Engl. J. Med.* **371**, 326–338 (2014).
50. Schett, G. *et al.* Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* **64**, 3156–3167 (2012).
51. Kavanaugh, A. *et al.* Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann. Rheum. Dis.* **73**, 1020–1026 (2014).
52. Edwards, C. J. *et al.* Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann. Rheum. Dis.* **75**, 1065–1073 (2016).
53. Wells, A. *et al.* SAT0382 Palace 4, a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, for treatment of psoriatic arthritis: long-term (52-week) improvements in physical function. *Ann. Rheum. Dis.* **73** (Suppl. 2), 732 (2014).
54. Celgene. Celgene Reports Fourth Quarter and Full Year 2015 Operating and Financial Results. *Celgene* http://ir.celgene.com/releasedetail.cfm?ReleaseID = 952157 (2016).
55. U.S. Food & Drug Administration. Information on biosimilars. *FDA* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm (2016).
56. Dörner, T. & Kay, J. Biosimilars in rheumatology: current perspectives and lessons learnt. *Nat. Rev. Rheumatol.* **11**, 713–724 (2015).
57. Putrik, P. *et al.* Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann. Rheum. Dis.* **73**, 198–206 (2014).
58. Ogdie, A. *et al.* Comprehensive treatment of psoriatic arthritis: managing comorbidities and extra-articular manifestations. *J. Rheumatol.* **41**, 2315–2322 (2014).
59. World Health Organization. *WHO handbook for guideline development* [online], http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf?ua = 1 (2012).

Author contributions

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