Non-steroidal anti-inflammatory drugs in psoriatic arthritis: clinical practice suggestions based on scientific evidence and expert opinion

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Abstract

Objective

The aim of this study was to provide evidence- and expert-based indications for the use of non-steroidal anti-inflammatory drugs (NSAIDs) in psoriatic arthritis (PsA).

Methods

A working group, composed of six rheumatologists with known expertise in the management of PsA and seven methodologists, identified key research questions related to NSAID use in PsA, which guided the systematic literature review (SLR) in Medline and Embase databases. RCTs and observational studies published until 26/1/2022 were included for efficacy and safety questions, respectively. Based on the results of the systematic search, the working group developed statements, which were evaluated by a multidisciplinary group of external reviewers through a Delphi exercise.

Results

The SLR retrieved only 7 manuscripts of interest, 5 RCTs and 2 observational studies. The drugs evaluated in the RCTs were indomethacin, diclofenac, ibuprofen, nimesulide, and celecoxib. These studies addressed peripheral joint involvement but not the other domains of PsA. Nimesulide and celecobix were reported to be significantly more effective than placebo in controlling joint inflammatory-related symptoms in the short-term. Based on this evidence and on expert opinion, the working group developed 12 statements on the use of NSAIDs in PsA.

Conclusion

This study provides a set of indications that may be helpful to the practicing rheumatologist in the prescription of NSAIDs for the relief of the symptoms due to the various clinical manifestations of PsA.

Key words

psoriatic arthritis, non-steroidal anti-inflammatory drugs, coxib, treatment

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of psoriatic arthritis (PsA). Both the European League Against Rheumatism (EULAR) (1) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (2) recommendations indicate that they may be used as first line of therapy for all the articular domains of PsA, especially in case of mild disease. In common practice, rheumatologists often prescribe NSAIDs to relieve symptoms at all stages of disease. However, the evidence about the efficacy of NSAIDs in PsA has not been systematically collected yet.

The purpose of this study was to provide indications for the use of NSAIDs in the treatment of PsA based on the evidence derived by a systematic literature review (SLR) and integrated by expert opinion.

Materials and methods

This study was set up by the steering committee of the "Study Group on Spondyloarthritis and Psoriatic Arthritis – Antonio Spadaro" of the Italian Society of Rheumatology (SIR). A working group was created, made up of the six members of the steering committee and a panel of seven methodologists (six junior rheumatologists led by a rheumatologist skilled in literature search who was also nominated study coordinator).

As a first step, the working group identified key topics related to NSAIDs use in PsA. From these topics they generated 8 questions on efficacy (4 questions regarding the use of NSAIDs as monotherapy and 4 questions regarding the use of NSAIDs as combination therapy with disease modifying anti-rheumatic drugs (DMARDs) in the domains of arthritis, dactylitis, enthesitis, and axial involvement), and 5 questions on safety regarding specific at-risk populations (elderly, patients with cardio-vascular risk factors, gastrointestinal comorbidities, renal comorbidities, and psoriasis) (Table I). These questions were then rephrased according to the Population, Intervention, Comparison, Outcome (PICO) strategy. The resulting PICOs guided the search strategy formulation and the selection of the published studies.

The SLR was performed in Medline and Embase databases, using two search strategies which combined keywords for NSAIDs and PsA and were differentiated for clinical questions regarding efficacy and safety of the treatment (See the Appendix). Only studies performed in patients with PsA were included; for studies including mixed populations, only those reporting data specifically related to PsA population were included. For the PICOs regarding efficacy, the search was limited to randomised controlled trials (RCTs) or non-randomised controlled trials, while the search strategy for the safety questions included also observational studies. Clinical cases and case-series were excluded. We included only studies published in full-text and in English until 26/1/2022. All search results were screened by two independent reviewers, and disagreements were resolved by consensus and discussion involving the study coordinator.

Data from the selected studies were extracted according to a pre-defined form and presented by summary tables during a web meeting. Risk of bias of controlled studies was assessed according to the Revised Cochrane risk-of-bias tool for randomised trials or crossover trials, according to study design (3); quality of observational study was evaluated through the Newcastle-Ottawa Quality Assessment Form for cohort studies or case-control studies (4). Based on the results of the SLR and according to the key clinical questions, the working group formulated the preliminary statements, which consisted in clinical practice suggestions for the use of NSAIDs in PsA. Where evidence from the SLR was not available for a key topic, statements were based on expert opinion. For every statement the level of evidence according to the Oxford Levels of Evidence was reported (5).

The draft of the statements developed by the working group was then submitted to a panel of external reviewers for validation through a Delphi process (6). The participants to the Delphi consultation were all members of the 'Study

Table I. Research questions regarding the use of NSAIDs in PsA.

no.	Research question	Statement
	Efficacy, monotherapy	
1	**1a.** In patients with PsA with peripheral joint arthritis, are NSAIDs in monotherapy more efficacious than no treatment/other analgesic treatment?	**1,2**
	1b. In patients with PsA with peripheral joint arthritis, is a NSAID in monotherapy more efficacious than another NSAID?	**9**
	1c. In patients with PsA with peripheral joint arthritis, is continuous treatment with a NSAID in monotherapy more efficacious than on-demand treatment?	**-**
	1d. In patients with PsA with peripheral joint arthritis, is long-term treatment with a NSAID in monotherapy more efficacious than short-term treatment?	**3**
2	**2a.** In patients with PsA with enthesitis, are NSAIDs in monotherapy more efficacious than no treatment/other analgesic treatment?	**5**
	2b. In patients with PsA with enthesitis, is a NSAID in monotherapy more efficacious than another NSAID?	**9**
	2c. In patients with PsA with enthesitis, is continuous treatment with a NSAID in monotherapy more efficacious than on-demand treatment?	**6**
	2d. In patients with PsA with enthesitis, is long-term treatment with a NSAID in monotherapy more efficacious than short-term treatment?	**-**
3	**3a.** In patients with PsA with dactylitis, are NSAIDs in monotherapy more efficacious than no treatment/other analgesic treatment?	**5**
	3b. In patients with PsA with dactylitis, is a NSAID in monotherapy more efficacious than another NSAID?	**9**
	3c. In patients with PsA with dactylitis, is continuous treatment with a NSAID in monotherapy more efficacious than on-demand treatment?	**6**
	3d. In patients with PsA with dactylitis, is long-term treatment with a NSAID in monotherapy more efficacious than short-term treatment?	**-**
4	**4a.** In patients with PsA with axial involvement, are NSAIDs in monotherapy more efficacious than no treatment/other analgesic treatment?	**7**
	4b. In patients with PsA with axial involvement, is a NSAID in monotherapy more efficacious than another NSAID?	**9**
	4c. In patients with PsA with axial involvement, is continuous treatment with a NSAID in monotherapy more efficacious than on-demand treatment?	**7**
	4d. In patients with PsA with axial involvement, is long-term treatment with a NSAID in monotherapy more efficacious than short-term treatment?	**7**
	Efficacy, combination therapy with cs/bDMARDs	
5	**5a.** In patients with PsA with peripheral joint arthritis treated with cs/bDMARDs, are NSAIDs more efficacious than no treatment/other analgesic treatment?	**4**
	5b. In patients with PsA with peripheral joint arthritis treated with cs/bDMARDs, is a NSAID more efficacious than another NSAID?	**9**
	5c. In patients with PsA with peripheral joint arthritis treated with cs/bDMARDs, is continuous treatment with a NSAID more efficacious than on-demand treatment?	**-**
	5d. In patients with PsA with peripheral joint arthritis treated with cs/bDMARDs, is long-term treatment with a NSAID more efficacious than short-term treatment?	**4**
6	**6a.** In patients with PsA with enthesitis treated with cs/bDMARDs, are NSAIDs more efficacious than no treatment/other analgesic treatment?	**-**
	6b. In patients with PsA with enthesitis treated with cs/bDMARDs, is a NSAID more efficacious than another NSAID?	**9**
	6c. In patients with PsA with enthesitis treated with cs/bDMARDs, is continuous treatment with a NSAID more efficacious than on-demand treatment?	**-**
	6d. In patients with PsA with enthesitis treated with cs/bDMARDs, is long-term treatment with a NSAID more efficacious than short-term treatment?	**-**
7	**7a.** In patients with PsA with dactylitis treated with cs/bDMARDs, are NSAIDs more efficacious than no treatment/other analgesic treatment?	**-**
	7b. In patients with PsA with dactylitis treated with cs/bDMARDs, is a NSAID more efficacious than another NSAID?	**9**
	7c. In patients with PsA with dactylitis treated with cs/bDMARDs, is continuous treatment with a NSAID more efficacious than on-demand treatment?	**-**
	7d. In patients with PsA with dactylitis treated with cs/bDMARDs, is long-term treatment with a NSAID more efficacious than short-term treatment?	**-**
8	**8a.** In patients with PsA with axial involvement treated with cs/bDMARDs, are NSAIDs more efficacious than no treatment/other analgesic treatment?	**-**
	8b. In patients with PsA with axial involvement treated with cs/bDMARDs, is a NSAID more efficacious than another NSAID?	**9**
	8c. In patients with PsA with axial involvement treated with cs/bDMARDs, is continuous treatment with a NSAID more efficacious than on-demand treatment?	**-**
	8d. In patients with PsA with axial involvement treated with cs/bDMARDs, is long-term treatment with a NSAID more efficacious than short-term treatment?	**-**
	Safety	
9	**9a.** In elderly patients with PsA, are NSAIDs safer than no treatment/other treatments?	
	9b. In elderly patients with PsA, is a NSAID safer than another NSAID?	**10**
10	**10a.** In patients with PsA with risk factors for cardio-vascular diseases, are NSAIDs safer than no treatment/other treatments?	
	10b. In patients with PsA with risk factors for cardio-vascular diseases, is a NSAID safer than another NSAID?	**10**
11	**11a.** In patients with PsA with renal comorbidities, are NSAIDs safer than no treatment/other treatments?	
	11b. In patients with PsA with renal comorbidities, is a NSAID safer than another NSAID?	**-**
12	**12a.** In patients with PsA with gastro-intestinal comorbidities, are NSAIDs safer than no treatment/other treatments?	
	12b. In patients with PsA with gastro-intestinal comorbidities, is a NSAID safer than another NSAID?	**11**
13	**13a.** In patients with PsA with cutaneous involvement, are NSAIDs safer than no treatment/other treatments?	
	13b. In patients with PsA with cutaneous involvement, is a NSAID safer than another NSAID?	**12**

Group on Spondyloarthritis and Psoriatic Arthritis - Antonio Spadaro' of the SIR, due to their expertise in PsA management. The external reviewers were asked to rate their agreement on every statement, using a 0-10 scale. Scores ≥7 were considered indicative of agreement. The statements which were not agreed upon by ≥70% of participants, were discussed in a subsequent dedicated face-to-face meeting and rephrased according to the participant' suggestions. The modified statements then underwent a second online Delphi round to be rated as reported above.

Results

The flow chart of the SLR is shown in Figure 1a-b. The SLR yielded 7 studies of interest: 5 controlled trials and 2 observational studies (7-13). The characteristics of these studies are reported in Table II.

Based on the results from the SLR and on expert opinion, 12 statements on the efficacy and safety of NSAIDs in PsA were developed. Then, the statements were sent to external reviewers (n=30) for validation; the response rate was 70% (n=21). Two statements (statement 2 and 8) did not reach the predefined level of agreement (≥70%) at the first Delphi round; therefore, they were rephrased during a face-to-face meeting and underwent a second Delphi round. The final statements, along with their level of agreement, are listed in Table III. Hereafter, we report a more detailed description of the evidence and opinions that led to formulation of the statements.

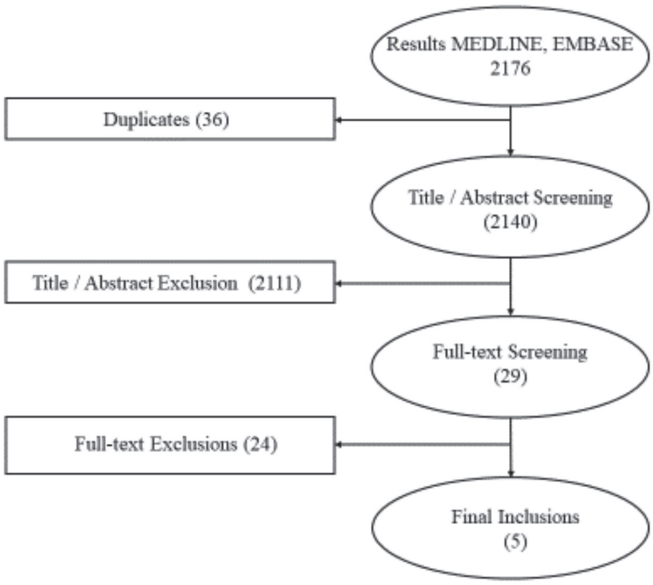

Fig. 1a. Steps in the SLR: efficacy

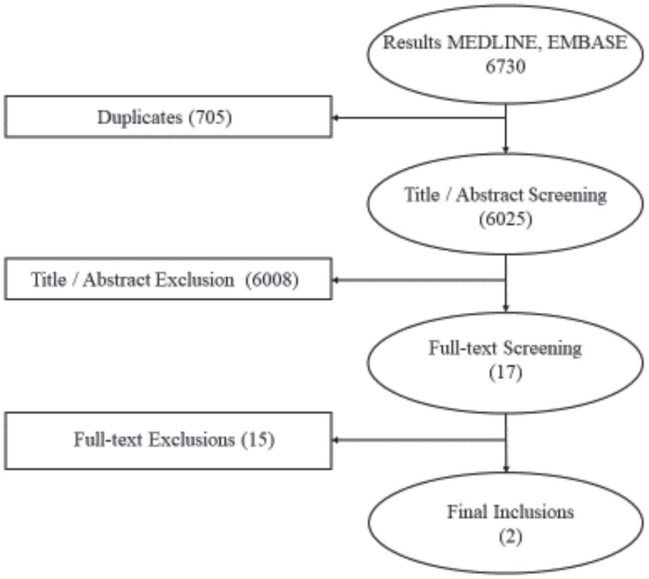

Fig. 1b. Steps in the SLR: safety

Statement 1. In patients with PsA with peripheral joint arthritis, monotherapy with either traditional NSAIDs or COX-inhibitors (COXIBs) may be effective in controlling joint pain.

In a 4-week RCT, 80 patients with active oligo or polyarticular PsA not treated with csDMARDs in the previous 3 months, were allocated to nimesulide 100 mg/day, nimesulide 200 mg/day, nimesulide 400 mg/day or placebo. A significantly higher reduction in the number of tender joints was observed for patients treated with nimesulide at all dosages compared with placebo (7). In another RCT, 609 patients with an articular flare due to PsA were randomised to receive celecoxib 400 mg, celecoxib 200 mg or placebo (8). After 2 weeks of treatment, the mean change from baseline in tender/painful joint score was significantly greater in patients receiving celecoxib compared to placebo.

A comparison between a NSAID and another treatment was performed only in one controlled study. This trial enrolled 40 patients with PsA who were randomised to receive etetrinate or ibuprofen, but only 11/20 of the etretinate group and 1/20 of the ibuprofen group completed the 24 weeks study period, providing insufficient data to obtain adequate evidence of a better efficacy of a treatment than another (9).

Statement 2. In patients with PsA with peripheral joint arthritis, monotherapy with either traditional NSAIDs or COX-IBs might reduce signs of joint inflammation.

In the trial assessing the efficacy of different dosages of nimesulide compared to placebo, a significantly higher reduction in the number of swollen joints was observed for patients treated with nimesulide (all dosages) compared to placebo (7). In the trial on celecoxib,

Table IIa. Characteristics of included studies: controlled studies.

First author, year	Study design	Patients	Intervention	Control group	Primary outcome	Time of outcome assessment (weeks)	Risk of bias
Lassus, 1976 (11)	Randomised, cross-over, double-blind trial	40	Indomethacin 25 mg x 2 (40)	Azapropazone 300 mg x 2 (40)	Overall assessment of efficacy	4+4	High
Leatham, 1982 (10)	Randomised, cross-over, double-blind trial	35	Indomethacin 25 mg x 3/50 mg x 3 (24)	Diclofenac 25 mg x3/50 mg x 3 (24)	Overall assessment of efficacy	4+4 (+2 run-in period)	High
Hopkins, 1985 (9)	Randomised, double-blind, parallel trial	40	Ibuprofen 400 mg x 4 (20)	Etretinate 0.5 mg/kg to 10 mg die (20)	VAS pain	24	High
Sarzi Puttini, 2001 (7)	Randomised, double-blind, placebo-controlled trial	80	Nimesulide 100 mg (20) Nimesulide 200 mg (20) Nimesulide 400 mg (20)	Placebo (20)	TJC/SJC/ PGA/PhGA	4	Low (with some concerns)
Kivitz, 2007 (8)	Randomised, double-blind, placebo-controlled trial	609	Celecoxib 400 mg (201) (primary) Celecoxib 200 mg (214) (secondary)	Placebo (194)	ACR20	12	Low (with some concerns)

VAS: visual analogue scale; TJC: tender joints count; SJC: swollen joints count; PGA: patient global assessment; PhGA: physician global assessment; ACR: American College of Rheumatology.

Table IIb. Characteristics of included studies: observational studies.

First author, year	Study design	Patients	Exposure	Primary outcome	Follow-up	Quality assessment
Dubreil, 2018 (12)	Nested case-control study	389	NSAID (diclofenac, naproxen)	Myocardial infarction	Not applicable	Poor quality
Lam, 2021 (13)	Retrospective cohort study	200	NSAID	First cardiovascular event	Mean follow-up: 8.8±3.8 years	Good quality

NSAID: non-steroidal anti-inflammatory drug.

after two weeks of treatment, the mean change from baseline in swollen joint score was significantly greater in patients receiving celecoxib compared to placebo (8).

This statement was modified after the first Delphi round and rephrased to underline the transient effect on signs of joint inflammation of NSAIDs, which should not be considered as a disease-modifying treatment for PsA.

Statement 3. In patients with PsA with peripheral joint arthritis, treatment with traditional NSAIDs or COXIBs should be prescribed only for short time periods (up to two weeks).

The SLR did not retrieve any study specifically assessing the comparative efficacy of short-term and long-term treatment with NSAIDs in PsA. However, the RCT evaluating the efficacy of celecoxib at different dosages against placebo demonstrated a significantly higher efficacy of celecoxib than placebo in controlling joint pain only in the short term (2 weeks) but not in the long term (at weeks 6 and 12) (8).

Statement 4. In patients with PsA with peripheral joint arthritis taking DMARDs, short term add on treatment with NSAIDs may be indicated for pain control and may be repeated in case of disease flare.

There are no studies specifically demonstrating that the combination of a DMARD with a NSAID is superior to a treatment with a DMARD alone in controlling joint pain due to PsA. However, in the RCT which demonstrated a higher efficacy of celecoxib than placebo in controlling pain due to articular flares in patients with PsA, a concomitant treatment with DMARDs was reported in 43–46% of patients (8). Therefore, based on indirect evidence and on expert opinion, the working group suggested that NSAIDs may be used in PsA patients on DMARD treatment who experience an arthritic flare.

Statement 5. There is no evidence concerning NSAID efficacy in the treatment of symptoms and inflammation related to enthesitis and dactylitis in patients with PsA. However, based on clinical experience, short-term treatment with NSAIDs may be used for the management of enthesitis and dactylitis-related symptoms.

The SLR did not retrieve any study specifically assessing the efficacy of NSAIDs

Table III. Clinical practice suggestions for the use of NSAIDs in PsA, based on scientific evidence and expert opinion.

	Statement	LoE	LoA, median (IQR)
1	In patients with PsA with peripheral joint arthritis, monotherapy with either traditional NSAIDs or COXIBs may be effective in controlling joint pain.	1	8 (5.5, 9)
2	In patients with PsA with peripheral joint arthritis, monotherapy with either traditional NSAIDs or COXIBs might reduce signs of joint inflammation.	1	8 (7.5, 9)
3	In patients with PsA with peripheral joint arthritis, treatment with traditional NSAIDs or COXIBs should be prescribed only for short time periods (up to two weeks).	5	8 (6.5, 9)
4	In patients with PsA with peripheral joint arthritis taking DMARDs, short term add on treatment with NSAIDs may be indicated for pain control and may be repeated in case of disease flare.	5	9 (8, 10)
5	There is no evidence concerning NSAID efficacy in the treatment of symptoms and inflammation related to enthesitis and dactylitis in patients with PsA. However, based on clinical experience, short-term treatment with NSAIDs may be used for the management of enthesitis and dactylitis-related symptoms.	5	8.5 (7, 9)
6	In patients with PsA with enthesitis and/or dactylitis, given the lack of evidence from clinical trials, continuous treatment with NSAIDs should not be preferred to on-demand use.	5	7 (5.5, 8)
7	There is no direct evidence concerning NSAID efficacy in the treatment of symptoms related to axial involvement in patients with PsA. However, based on clinical experience and on data from patients with ankylosing spondylitis, NSAIDs may be used for the management of axial-related symptoms both in the short and long term.	5	8 (7, 9)
8	In patients with PsA who do not respond to a first NSAID, a second NSAID may be considered.	5	8 (6, 8.5)
9	Given the lack of evidence concerning the higher efficacy of one NSAID over another in PsA, the choice of the NSAID should be based on its safety profile.	5	8 (7, 9)
10	In patients with PsA carrying cardio-vascular risk factors (age over 65 included), analgesics should be preferred over NSAIDs. In case of symptoms persistence, traditional NSAIDs should be preferred over COXIBs.	5	8 (6.5, 9)
11	In patients with PsA with history of gastro-esophageal reflux disease, gastro-duodenitis, and gastro-duodenal ulcer, COXIBs should be preferred to traditional NSAIDs. If traditional NSAIDs are used, gastro-protection should be recommended.	5	9 (8, 10)
12	As there is no evidence of psoriasis worsening due to NSAIDs in patients with PsA, their use is not contraindicated in these patients.	5	9 (8, 9.5)

LoE: level of evidence; LoA; level of agreement; IQR: interquartilic range; PsA: psoriatic arthritis; NSAID: non-steroidal anti-inflammatory drug; COXIB: COX-inhibitor.

on enthesitis or dactylitis in patients with PsA. However, based on expert opinion and according to international guidelines (2), the use of NSAIDs may be considered an option for symptoms relief due to enthesitis and/or dactylitis.

Statement 6. *In patients with PsA with enthesitis and/or dactylitis, given the lack of evidence from clinical trials, continuous treatment with NSAIDs should not be preferred to on-demand use*.
Given the absolute lack of evidence on this topic, based on clinical experience and on safety issues related to long-term treatment, the working group suggested that in patients with enthesitis and/or dactylitis continuous treatment with NSAIDs is less advisable than on-demand use.

Statement 7. *There is no direct evidence concerning NSAID efficacy in the treatment of symptoms related to axial involvement in patients with PsA. However, based on clinical experience and on data from patients with ankylosing spondylitis, NSAIDs may be used for the management of axial-related symptoms both in the short and long term*.
As the SLR did not find any study specifically focused on axial involvement in PsA, the working group deemed appropriate to consider the recommendations for the use of NSAIDs in axial spondyloarthritis (SpA). Even though the two clinical entities are not completely overlapping, a similar disease burden is described so that an analogous response to NSAID therapy is predictable (14). In patients with axial SpA and predominant axial involvement, NSAIDs are suggested as first-line pharmacological treatment (15-16). The choice of the dose and the duration of the treatment should consider both efficacy and safety, with an ongoing monitoring of risk factors (17). Continuous use is generally preferred to on-demand use, even though a higher efficacy of continuous use in slowing radiographic progression was not clearly demonstrated and the safety profile should be carefully monitored (18-21).

Statement 8. *In patients with PsA who do not respond to a first NSAID, a second NSAID may be considered*.
This statement in only based on expert opinion and underlines the possible individual response to NSAIDs with

different molecular structure. The statement underwent two rounds of external rating and was rephrased to avoid misunderstandings: the choice of a second NSAID should not be intended as alternative to a disease-modifying therapy and must not delay the start of a treatment with a DMARD.

Statement 9. Given the lack of evidence concerning the higher efficacy of one NSAID over another in PsA, the choice of the NSAID should be based on its safety profile.

The literature revision revealed only two studies comparing the efficacy of different NSAIDs (indomethacin *vs*. diclofenac; indomethacin *vs*. azapropazone) (10-11). Both are small-sized and at high risk of bias and did not show significant differences between the two studied NSAIDs. Moreover, azapropazone has been withdrawn from the market and consequently was excluded from the analysis. Therefore, the experts stated that the choice of the NSAID in every single patient should be guided by patient's characteristics (*i.e*. age, comorbidities), related to the safety profile of the selected drug. For safety issues, prescribing physicians should refer to the specific drug adverse events reported in the summary of product characteristics to be informed of potential risks and contraindications related to each drug.

Statement 10. In patients with PsA carrying cardio-vascular risk factors (age over 65 included), analgesics should be preferred over NSAIDs. In case of symptoms persistence, traditional NSAIDs should be preferred over COXIBs.

The cardiovascular risk associated with NSAID use in patients with inflammatory arthritis has been extensively studied. Therefore, the panel stated to set a specific statement for patients carrying cardio-vascular risk factors, such as for example older age, previous cardio-vascular events, smoking, obesity, dyslipidaemia, diabetes, metabolic syndrome, hyperuricaemia, subclinical atherosclerosis (22).

The systematic literature search identified two cohort studies which provided data specifically on the PsA population. A retrospective observational study involving 200 patients with PsA showed a protective effect of NSAIDs on cardiovascular risk; in the sub-group analysis, only non-selective NSAIDs use was associated with lower risk of CV events, while no significant association was found for COX2 inhibitors (12). A case-control observational study on the risk of myocardial infarction (MI) in 8140 patients with SpA and osteoarthritis, showed that in SpA patients diclofenac use was significantly associated with higher MI risk (OR 3.32, 1.57-7.03), while naproxen was not. However, a sub-analysis limited to PsA patients did not reveal any significant association between NSAID use and MI (13).

Statement 11. In patients with PsA with history of gastro-esophageal reflux disease, gastro-duodenitis, and gastro-duodenal ulcer, COXIBs should be preferred to traditional NSAIDs. If traditional NSAIDs are used, gastro-protection should be recommended.

The SLR did not find any study specifically investigating this topic in patients with PsA. However, based on the well-known gastro-intestinal safety profile of NSAIDs, the experts suggest preferring COXIBs to traditional NSAIDs in patients at risk of gastrointestinal bleeding and associating a gastro-protection when using traditional NSAIDs.

No specific indications were given for patients with concomitant inflammatory bowel disease (IBD), but the prescribing rheumatologist should be aware of the risks of NSAID treatment in patients with IBD and should refer to the treating gastroenterologist for its use in these subjects.

Statement 12. As there is no evidence of psoriasis worsening due to NSAIDs in patients with PsA, their use is not contraindicated in these patients.

A possible detrimental effect of NSAID treatment on skin involvement was suggested in old studies on patients with psoriasis, but this topic was not specifically assessed in studies performed on patients with PsA. Indirect evidence comes from some studies included in our SLR, which analysed as a secondary outcome the efficacy of NSAID on PASI score, without identifying a worsening of psoriasis associated with the treatment (7, 8). Therefore, the expert panel did not provide a contraindication to NSAID use in patients with PsA and significant cutaneous involvement.

Discussion

NSAIDs are widely used in clinical practice to relieve symptoms of PsA but, as confirmed by the SLR performed in this study, the evidence supporting their efficacy and safety in this rheumatic disorder is limited. However, practicing rheumatologists consider NSAIDs potentially effective in all the musculoskeletal domains of PsA and international recommendations for the treatment of this disorder suggest their use, often as first step of therapy (1, 2). To provide a guidance on the use of NSAIDs in PsA, the Study Group on Spondyloarthritis and Psoriatic Arthritis of the SIR, decided to elaborate a set of indications based on the available evidence and completed by expert opinions validated through a Delphi exercise. The main strength of this project is that the SLR was specifically focused on the population of patients affected by PsA. Even if this choice could have limited the amount of data available, the SLR provided specific data on NSAIDs' efficacy and safety in the PsA population, which could be different from that observed in the entire SpA population (from which indications for PsA are usually extrapolated).

The SLR retrieved only five RCTs, all published more than 15 years ago, and only two of them with a low risk of bias (7, 8). Overall, these studies showed that NSAIDs were more effective than placebo in controlling symptoms due to joint inflammation, without pointing out a higher efficacy of a specific NSAID than another. We did not find any study specifically addressing the efficacy of these compounds on enthesitis and dactylitis; however, experts' opinions, in line with international guidelines, suggest that NSAIDs could be effective on these disease manifestations (1, 2). Similarly, no specific data on NSAID efficacy on psoriatic spondylitis emerged from the SRL; treatment indications were extrapolated from

those provided for axial SpA because, despite possible significant differences in clinical manifestations and underlying pathogenetic mechanisms between axial involvement in PsA and SpA, it is reasonable to predict a similar symptomatic efficacy of these drugs in both these clinical entities (1, 2, 14, 23-25). However, a recent cohort study suggests that the percentage of patients who respond to NSAID treatment may be lower in PsA with axial involvement than in axial SpA (26).

NSAIDs were identified as an effective therapeutic option in case of a flare of the disease, both as monotherapy and in association with DMARDs. As for treatment duration, however, the experts suggest not to use them as long-term therapy, but only on demand, for a maximum of two weeks. This indication was based on the lack of evidence on their long-term efficacy, on the conviction that they are not effective in controlling disease progression, and on their safety issues. On the other hand, in case of axial involvement, based on the axial-SpA data, the experts suggest that even long-term therapy may be considered (16).

The statements which suggested, in case of a failure of a NSAID, to try another one, is an indication entirely based on expert opinion, due to the possible individual response to NSAIDs with different molecular structure. This statement was modified from the original version during Delphi exercise to underline that NSAID should not delay the start of a DMARD in PsA, unlike in axial SpA, for which ASAS-EULAR recommendations suggest at least two courses of NSAIDs at the appropriate dosage before considering a bDMARD (16).

As there is no evidence of the higher efficacy of a NSAIDs over another, the experts suggested to choose the drug on the basis on its safety profile. The SLR retrieved only a few studies specifically assessing the safety of NSAIDs in PsA patients, therefore the opinion on this issue was mostly based on the well-known possible adverse events of this class of drugs. For safety issues not specifically addressed by our SLR or for which no evidence emerged from our SLR, the experts suggested that prescribing physicians refer to the specific drug adverse events reported in the summary of product characteristics to be aware of contraindications related to each drug.

We formulated a specific statement concerning the efficacy of NSAIDs in patients with relevant skin involvement, because previous studies reported a possible exacerbation of cutaneous manifestations of psoriasis during NSAID treatment (27-29); however, this finding was not replicated in studies emerging from our SLR, therefore the experts stated that psoriasis should not be considered a contraindication to NSAIDs use.

The safety profile of NSAID during pregnancy and lactation was not specifically assessed by our SLR. However, recent national and international recommendations regarding reproductive issues in women with inflammatory arthritis suggest that women who are desiring pregnancy may consider NSAID discontinuation before conception, because reversible female infertility associated with NSAID treatment was described in patients with inflammatory arthritis, and strongly recommend against the use of NSAID in the third trimester of pregnancy due to the increased risk of premature closure of the ductus arteriosus (30-36).

The main limitation of these treatment indications is that they are largely based on expert's opinion, due to the little evidence available on the subject. However, the Delphi methodology is considered an acceptable way to provide guidance in case of weak evidence (6).

In conclusion, this document may be of support to practicing rheumatologist in prescribing NSAIDs among the various clinical manifestations of PsA. The main indication provided by this study is that both traditional NSAIDs and COXIBs may help in easing the symptoms of all the articular manifestations of PsA, and that safety profile should be a major driver for the choice of the best treatment for each individual patient.

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Appendix

Search strategy:
Medline (via Pubmed)

Efficacy

(((Arthritis, Psoriatic) OR ("Arthritis, Psoriatic"[Mesh])) OR (psoria* AND (arthr* or polyarthr* or polyarthr* or oligoarthr* or oligo-arthr* or rheumat*))) AND (((((Anti-Inflammatory Agents, Non-Steroidal) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) OR (nsaid*)) OR (Aceclofenac OR (Acetylsalicylic acid) OR acephen OR Ampyrone OR Amynopirin OR Antipyrine OR Apazone OR Aspirin OR Bufexamac OR Clofazimine OR Clonixin OR Curcumin OR Dexketoprofen OR Dexibruprofen OR Diclofenac OR Diflunisal OR Dipyrone OR Epirizole OR Etodolac OR Fenbufen OR Fenclofenac OR Fenoprofen OR Floctafenine OR Flurbiprofen OR Ibuprofen OR Indomethacin OR Ketoprofen OR Ketorolac OR Lederfen OR (Meclofenamic Acid) OR (Mefenamic Acid) OR Mesalamine OR Nabumetone OR Naproxen OR (Niflumic Acid) OR Oxaprozin OR Oxyphenbutazone OR Phenazone OR Phenylbutazone OR Piroxicam OR pirazolac OR pirprofen OR Ponstan OR Prenazone OR Salicylate* OR Salsalate OR Seractil OR Sulfasalazine OR Sulindac OR Suprofen OR Tenoxicam OR (Tiaprofenic acid) OR (tolfenamic acid) OR Tolmetin OR ximoprofen)) OR ((((((Cyclooxygenase 2 Inhibitor*) OR ("Cyclooxygenase 2 Inhibitors"[Mesh] AND "Cyclooxygenase 2 Inhibitors" [Pharmacological Action])) OR (cox 2 inhibitor*)) OR (cyclo-oxygenase-2 inhibitor*)) OR (meloxicam or movalis or mobec or mobic or movicox or mobicox or parocin or uticox or etoricoxib or arcoxia or celecoxib or celebrex)) OR (coxib*)))

Filters: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review

Safety

(((Arthritis, Psoriatic) OR ("Arthritis, Psoriatic"[Mesh])) OR (psoria* AND (arthr* or polyarthr* or poly-arthr* or oligoarthr* or oligo-arthr* or rheumat*))) AND (((((Anti-Inflammatory Agents, Non-Steroidal) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) OR (nsaid*)) OR (Aceclofenac OR (Acetylsalicylic acid) OR acephen OR Ampyrone OR Amynopirin OR Antipyrine OR Apazone OR Aspirin OR Bufexamac OR Clofazimine OR Clonixin OR Curcumin OR Dexketoprofen OR Dexibruprofen OR Diclofenac OR Diflunisal OR Dipyrone OR Epirizole OR Etodolac OR Fenbufen OR Fenclofenac OR Fenoprofen OR Floctafenine OR Flurbiprofen OR Ibuprofen OR Indomethacin OR Ketoprofen OR Ketorolac OR Lederfen OR (Meclofenamic Acid) OR (Mefenamic Acid) OR Mesalamine OR Nabumetone OR Naproxen OR (Niflumic Acid) OR Oxaprozin OR Oxyphenbutazone OR Phenazone OR Phenylbutazone OR Piroxicam OR pirazolac OR pirprofen OR Ponstan OR Prenazone OR Salicylate* OR Salsalate OR Seractil OR Sulfasalazine OR Sulindac OR Suprofen OR Tenoxicam OR (Tiaprofenic acid) OR (tolfenamic acid) OR Tolmetin OR ximoprofen)) OR ((((((Cyclooxygenase 2 Inhibitor*) OR ("Cyclooxygenase 2 Inhibitors"[Mesh] AND "Cyclooxygenase 2 Inhibitors" [Pharmacological Action])) OR (cox 2 inhibitor*)) OR (cyclo-oxygenase-2 inhibitor*)) OR (meloxicam or movalis or mobec or mobic or movicox or mobicox or parocin or uticox or etoricoxib or arcoxia or celecoxib or celebrex)) OR (coxib*)))

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