Rheumatology RESEARCH REVIEW™

Making Education Easy

Issue 41 – 2021

In this issue:

Abbreviations used in this issue

ANCA = antineutrophilic cytoplasmic autoantibody
HLA = human leucocyte antigen
MVA = motor vehicle accident
OA = osteoarthritis
OR = odds ratio
PPI = proton-pump inhibitor
PRO = patient-reported outcome
RA = rheumatoid arthritis
SpA = spondyloarthritis
VAS = visual analogue scale

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Welcome to issue 41 of Rheumatology Research Review.

A retrospective review reporting that febuxostat was efficacious and well tolerated in dialysis patients with gout begins this issue. There is also a paper investigating factors associated with the presence and extension of spinal and sacroiliac joint lesions on MRI that suggest the presence of axial SpA in the general population aged <45 years. This is followed by research suggesting that the coexistence of psoriasis in patients with SpA is associated with differences in clinical expression of SpA, a greater disease burden and increased medication use. This issue concludes with a randomised trial from our Australian neighbours assessing the efficacy of an intervention of a combination of education on self-management and ergonomic principles, a base-of-thumb splint, hand exercises and diclofenac sodium gel for the management of thumb-base OA.

We hope you enjoy this update in rheumatology research. We always appreciate any feedback or comments you wish to send us.

Kind regards,

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Efficacy and tolerability of febuxostat in gout patients on dialysis

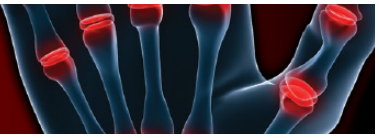
Authors: Choi SY et al.

Summary: This retrospective study investigated the efficacy and tolerability of febuxostat in patients with gout on dialysis. Clinical and laboratory data available for patients with gout who initiated febuxostat during dialysis were assessed. Data regarding serum uric acid levels before and after febuxostat, gout attacks and adverse events were obtained from medical records. The patients received febuxostat for >3 months (n=45 haemodialysis; n=17 peritoneal dialysis). Mean serum uric acid level was significantly reduced 3 months after treatment versus pretreatment (3.71 vs. 9.36 mg/dL [p<0.001]). Both haemodialysis and peritoneal dialysis patients achieved a significant reduction in serum uric acid level at 3 months, which remained low for 12 months. Two patients discontinued febuxostat due to adverse effects. Febuxostat 80 mg/day was associated with more adverse effects than 20–40 mg/day (OR 8.25 [95% CI 1.90, 35.97]).

Comment (AH): The management of gout with urate-lowering therapy in patients with severe chronic kidney disease can be problematic. Allopurinol undergoes predominantly renal clearance, requiring dosage reduction that can reduce the effectiveness of treatment. As febuxostat is predominantly metabolised in the liver, it might be a more suitable urate-lowering therapy in dialysis patients. This study documents the outcomes of 62 patients who commenced febuxostat while undergoing haemodialysis or peritoneal dialysis for end-stage chronic kidney disease. In general, lower than usual starting doses were chosen, and improvements in serum urate levels and frequency of gout attacks were seen in the majority of patients. A target urate level of ≤6.0 mg/dL (0.36 mmol/L) was achieved in 87%. Patients starting at 80 mg/day were more likely to experience adverse events than those starting at 20–40 mg/day (OR 8.25 [95% CI 1.90, 35.97]). This study demonstrates the effectiveness of febuxostat as a urate-lowering therapy in dialysis patients, and makes a case for a low initial dose, titrating up as necessary.

Reference: Intern Med J 2021;51:348–54

Abstract



The oral and gut microbiome in rheumatoid arthritis patients

Authors: Chu X-J et al.

Summary: This systematic review of 26 publications included ≥3 that reported decreased *Faecalibacterium* in the gut, and also ≥3 reporting decreased *Streptococcus* and *Haemophilus* and increased *Prevotella* in the oral cavities, of patients with early RA or RA compared with healthy controls. There was also evidence of some *Prevotella* spp. being increased in the oral cavities of patients with RA. The oral cavities of patients with RA had increased or unchanged microbiome α-diversity, whereas in their gut, microbiome α-diversity was more commonly either decreased or unchanged.

Comment (SS): In this review the authors performed a systematic review to investigate the oral and gut microbiome in patients with RA. The review would have benefited from a clearer statement of aims, and the combination of both gut and oral microbiome analyses gives it an overwide reach. Analysis of the gut microbiome is very challenging. A recent study of the human gut microbiome identified 4644 unique gut microbes. The metabolic activity of these microbes can differ between individuals or populations and may exert influence on the host. The term dysbiosis is used to describe transient or permanent changes in the microbiome that may contribute to disease, particularly a shift of the mucosa-associated microbiota to a more pro-inflammatory profile. Several attempts to quantify such perturbations have been made, using scoring systems, but most are controversial. Several studies have suggested that the microbiome may have a role in the aetiology or perpetuation of RA, especially the resident microbiota of the gut and oral cavity. The authors found 26 studies to include in their analysis. Most studies included were small with under 100 participants, and controls groups of OA or healthy controls. The results were inconsistent across the studies, but seem to suggest a loss of gut microbial diversity with increasing disease duration. In the oral cavity, several studies support an increased abundance of *Prevotella* spp., but this may simply indicate the increased prevalence of periodontitis in RA. Overall this review highlights the lack of data and the difficulties of delineating cause and effect in terms of shifts in diversity. It seems unlikely that specific organisms have a universal role in precipitating or perpetuating RA. Whether dysbiosis has a role in the aetiology or severity and flares in RA remains to be shown.

Reference: Rheumatology 2021;60:1054–66
Abstract

Serious infections in ANCA-associated vasculitides in the biologic era

Authors: Thomas K et al.

Summary: These researchers assessed the incidence of and risk factors for serious infections in a retrospective real-world cohort of 162 patients with ANCA-associated vasculitides (63% with granulomatosis with polyangiitis, 37% with microscopic polyangiitis, 86% ANCA-positive and 80% with generalised disease) from three tertiary referral centres. During 891.2 patient-years of follow-up, there were 67 serious infections recorded affecting 50 patients (incidence rate 7.5 per 100 patient-years). The incidence rate was higher during induction with cyclophosphamide versus rituximab (19.3 vs. 11.3 per 100 patient-years) but lower and comparable between maintenance rituximab versus other regimens (5.52 vs. 4.54 per 100 patient-years). A multivariate analysis revealed that plasmapheresis and/or dialysis was a predictor for a serious infection both during the first year postdiagnosis and during the follow-up period (respective ORs 3.16 [95% CI 1.001, 9.96] and 5.21 [1.93, 14.07]), and a higher baseline Birmingham Vasculitis Activity Score was a predictor of serious infection only during the first year (1.11 [1.01, 1.21]).

Comment (AH): This study sought to determine the risk factors for serious infection in a cohort of patients with ANCA-associated vasculitis. It reported a relatively low incidence of serious infection, possibly due to less use of cyclophosphamide and prolonged use of corticosteroids than in previous studies. The risk of serious infection was greatest in the first year of treatment, when it was four times higher than in the late stage of treatment. Patients undergoing induction with cyclophosphamide were more likely to have a serious infection than with rituximab induction. In the maintenance phase there was no difference in risk of serious infection in those treated with rituximab compared with azathioprine. Disease-related risk factors for serious infection included high baseline disease activity, and early need for plasma exchange and/or dialysis. Eosinophilic granulomatosis with polyangiitis patients were excluded due to the heterogeneous nature of that disease. The retrospective nature of the study could have underestimated the infection risk, but the study sample is a reasonable size for this disease and the mean follow-up of five and a half years is adequate to compare early and late treatment phases.

Reference: Arthritis Res Ther 2021;23:90
Abstract

Which factors are associated with bone marrow oedema suspicious of axial spondyloarthritis as detected by MRI in the sacroiliac joints and the spine in the general population?

Authors: Baraliakos X et al.

Summary: The objective of this population-based cohort study was to identify factors associated with the presence and extension of spinal and sacroiliac joint MRI lesions suggestive of axial SpA. Spinal T1/T2 and sacroiliac joint MRIs of 793 volunteers were evaluated, and the presence and extension of bone marrow oedema were captured. The presence of sacroiliac joint bone marrow oedema was strongly associated with delivery during the last year (OR 4.47 [CI 1.49, 13.41]). For sacroiliac joint bone marrow oedema extension, associations were found with delivery during the last year (incidence rate ratio 4.52 [95% CI 1.48, 13.84]), HLA-B27 positivity (2.32 [1.30, 4.14]), BMI 25–30 vs. <25 kg/m^2 (1.86 [1.19. 2.89]) and back pain in the prior 3 months (1.55 [1.04, 2.31]). For spinal bone marrow oedema, associations were found for age per decade (OR 1.46 [95% CI 1.13, 1.90]) and physically demanding work (1.46 [1.06, 2.00]). These findings support the hypothesis that mechanical strain contributes to bone marrow oedema in the general population aged <45 years and that HLA-B27 positivity is a severity factor rather than a susceptibility factor for sacroiliac joint bone marrow oedema.

Comment (SS): MRI has become the standard investigation for determining active sacroiliitis in patients with suspected SpA. However, the presence of bone marrow oedema at the sacroiliac joints on MRI is notoriously difficult to interpret, and there has been a growing realisation that bone marrow oedema is not uncommon in the general population and far from diagnostic of SpA. In this important study, 793 MRI scans were performed on healthy volunteers, with scans read by two trained, blinded readers. All participants were under 45 years old and the gender split was equal. The population prevalence of HLA-B27 was 8.2%, in line with that expected in Northern European populations. The strongest correlations were with recent pregnancy and childbirth within the last 12 months (OR ~4.5). Lesser associations were seen with overweight/obesity, back pain in the last 3 months and HLA-B27 positivity. Interestingly, in this group, HLA-B27 did not seem to be a susceptibility marker for bone marrow oedema at the sacroiliac joints, but did predict the severity of changes. The prevalence of bone marrow oedema at the sacroiliac joints was unfortunately not clearly presented in the study, although this was a self-selecting group. However, the data do support mechanical strain as a cause of bone marrow oedema at the sacroiliac joints. There were fewer than ten participants who fulfilled criteria for axial SpA, but classification of patients as having axial SpA was not an aim of the study. In summary, these data support the need for caution in interpreting MRI changes of bone marrow oedema and identify groups with a higher prevalence of these changes. This study will help with interpreting sacroiliac joint changes in the context of the clinical presentation.

Reference: Ann Rheum Dis 2021;80:469–74
Abstract

Axial and peripheral spondyloarthritis: does psoriasis influence the clinical expression and disease burden?

Authors: López-Medina C et al.

Summary: This analysis of data from the Spanish REGISPONSER registry aimed to elucidate how concurrent psoriasis impacts disease burden in SpA. A total of 2296 patients were included in the study. Pair-wise analyses compared outcomes for patients with axial or peripheral phenotypes with/without psoriasis (cutaneous or nail involvement). Regardless of axial or peripheral SpA phenotype, the presence of psoriatic manifestations was associated with a greater disease burden, worse PROs and greater medication use. Differences in clinical symptoms of disease were also found with psoriatic involvement; patients with the axial phenotype had reduced odds of uveitis (OR 0.46) but increased odds of synovitis and dactylitis (2.59 and 2.78, respectively), and patients with the peripheral phenotype showed reduced odds of heel enthesitis (0.22). Psoriasis in both SpA phenotypes had an independent association with HLA-B27 positivity (respective ORs 0.27 and 0.14).

Comment (AH): Over the last 50 years, the classification of SpA has been progressing steadily, with notable waypoints that include the Moll and Wright classification of psoriatic arthritis, the New York criteria for ankylosing spondylitis, and more recently the CASPAR, ASAS and ESSG criteria. Increasingly, we are seeing the tight partitions between diseases dissolving with the emergence of the modern paradigm that SpA is an entity with a range of clinical, genetic and radiographical features that determine the phenotype. This study took data from a disease registry to attempt to determine whether the presence of psoriasis has any specific implications for the way that SpA manifests, or if is it just a cutaneous epiphenomenon. In spite of the uncomfortable feeling that the presence of psoriasis may have led the treating doctors to earlier diagnosis or more intensive treatment, it does appear that axial SpA patients with psoriasis had lower prevalence of HLA-B27 and the associated uveitis than those axial SpA patients without psoriasis. Or was psoriasis just a substitute for HLA-B27 and uveitis in meeting the criteria for diagnosis? Likewise, there was a greater prevalence of synovitis, dactylitis and greater use of oral conventional synthetic DMARDs (disease-modifying antirheumatic drugs) than non-psoriatic axial SpA patients (possibly because these drugs are recommended in psoriatic arthritis but not in ankylosing spondylitis). These reservations aside, it does appear that psoriatic axial and peripheral SpA, while not necessarily distinct diseases from their non-psoriatic counterparts, do run different courses with differences in manifestations and severity.

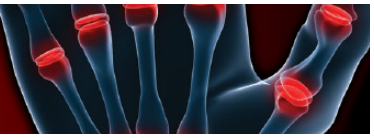
Reference: Rheumatology 2021;60:1125–36
Abstract

Independent commentary by Associate Professor Simon Stebbings

Simon Stebbings qualified from University College London. He is a Consultant Rheumatologist at Dunedin Hospital and Associate Professor at Dunedin School of Medicine, University of Otago. His research interests include the pathogenesis of ankylosing spondylitis and the development of outcome measures in rheumatic disease.

Independent commentary by Associate Professor Andrew Harrison

Andrew Harrison is a rheumatologist based in Wellington, Associate Professor in Medicine at the University of Otago Wellington, and Clinical Leader of Research at Capital & Coast District Health Board. He is an Otago graduate and obtained his PhD from the Royal Postgraduate Medical School in London. His research interests include the basic cellular and molecular mechanisms of inflammation, the genetics of gout and rheumatoid arthritis, and access to healthcare resources.



Acceptability and content validity of patient-reported outcome measures considered from the perspective of patients with rheumatoid arthritis

Authors: Shaw Y et al.

Summary: These researchers assessed the acceptability and content validity of PRO measures commonly used in RA by describing the perceptions of 18 patients regarding PRO measures and comparing their responses on PRO measures with their verbal accounts of disease impacts. Only a few of the patients made positive comments about PRO measures, with most doubting that PRO measures would be sufficient to accurately convey their experiences regarding symptoms and functional limitations. Patients discussed the ease of responding to questions and capturing and conveying symptoms, and expressed concerns regarding symptom under-reporting and interpretation of responses. Compared with verbal accounts, the personal significance of limitations were not often conveyed by PRO measures, but PRO measures were able to detect limitations that were omitted or insufficiently described during interviews. Verbal accounts of pain were able to be categorised into three levels of severity (namely, pain without interference in activities, pain is not the worst ever experienced but interferes with activities, and pain is omnipresent), but pain VAS scores were more effective for communicating pain severity in finer gradations.

Comment (SS): This interesting study used mixed-method qualitative and questionnaire data to explore patient perspectives of PRO measures. The 'treat-to-target initiative' was one incentive for such measures to be introduced into routine clinic assessments, and in some countries, such as Denmark, this approach has been used nationally for many years. Anecdotally, many patients express frustration with PROs and find them difficult to complete. Studies, however, show that commonly used PROs, such as the HAQ disability index, can be useful in monitoring progression or improvement in a semi-quantifiable way. In this study, a small number of patients (n=18; predominantly female) underwent an intensive 3-hour interview after completing commonly used PROs including the HAQ score, SF-36, VAS pain fatigue and sleep and FACIT-F fatigue score. Thematic analysis identified four main themes relating to PROs: i) comprehensibility and answerability of PRO measures; ii) capacity of PRO measures to capture the patient's experience of symptoms; iii) concerns about the under-reporting of symptoms; and iv) concerns about the interpretation of responses. PROs such as the HAQ assessed the extent of functional limitations, but did not capture the significance of limitations in the context of the patient's life, such as effects on recreational activities, fashion choices and ability to care for family members. Some patients felt frustrated and doubted the validity of the questionnaires. A range of commonly used questionnaires may not adequately reflect the limitations experienced by those with RA, including the HAQ, FACIT-Fatigue, EQ-5D and SF-36. PROs still have an important role in characterising burden of disease, allowing semi-quantitative longitudinal measures that can inform clinical decisions. However, questionnaires such as the HAQ, FACIT-F and SF-36 were developed 30–40 years ago and did not undergo the rigorous item analysis likely to be undertaken today, particularly involving patient input. A systematic approach to developing better PROs is a way forward, such as that recently undertaken to develop the Assessment in Spondyloarthritis International Society Health Index (the ASAS-HI). This included an additional questionnaire looking a patient's individual life context.

Reference: Arthritis Care Res 2021;73:510–9
Abstract

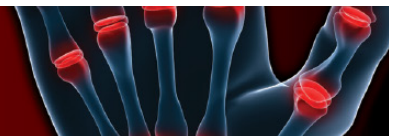
Tocilizumab vs placebo for the treatment of giant cell arteritis with polymyalgia rheumatica symptoms, cranial symptoms or both in a randomized trial

Authors: Spiera R et al.

Summary: This was a *post hoc* analysis of the GiACTA trial, which randomised 250 patients with giant cell arteritis to receive tocilizumab weekly or every other week plus a 26-week prednisone taper or placebo plus a 26- or 52-week prednisone taper. For the respective subgroups of participants with polymyalgia rheumatica symptoms only (n=52), cranial symptoms only (n=94) and both types of symptoms (n=104), tocilizumab recipients had higher 52-week sustained remission rates than placebo recipients (45.2% vs. 19.0% [p=0.0446], 60.3% vs. 19.4% [p=0.0001] and 55.0% vs. 11.4% [p<0.0001], respectively), and smaller proportions of tocilizumab recipients experienced disease flare (41.9% vs. 57.1%, 20.7% vs. 47.2% and 31.7% vs. 81.8%). The annualised flare rate and risk of flare were both significantly lower among tocilizumab versus placebo recipients for participants with cranial symptoms only and both types of symptoms; these were nonsignificantly numerically lower in the subgroup with polymyalgia rheumatica symptoms only.

Comment (AH): The efficacy and safety of tocilizumab in giant cell arteritis have been established in two clinical trials. This study is a *post hoc* analysis of the GiACTA trial, in which patients with an established diagnosis of giant cell arteritis had presented with polymyalgia rheumatica symptoms alone (i.e. no cranial symptoms), with cranial symptoms alone, or with a mixture of polymyalgia rheumatica and cranial symptoms. The main finding of the study was that in all three groups, sustained remission was achieved in a significantly higher proportion of patients treated with tocilizumab than placebo. Consequently, median cumulative doses of prednisone were lower in the tocilizumab group than in the placebo group. This finding is significant because modern imaging techniques have allowed a diagnosis of giant cell arteritis in the absence of the classical cranial symptoms. It is reassuring to see that tocilizumab has efficacy not just in cranial disease, but also across the emerging spectrum of manifestations of this disease.

Reference: Semin Arthritis Rheum 2021;51:469–76
Abstract



Driving ability and safety in rheumatoid arthritis

Authors: Zhou DJ et al.

Summary: This systematic review included 22 studies in a total of 6285 patients with RA reporting quantitative data on the association between RA and driving ability and/or the use of assistive devices or modifications to improve driving ability. There was considerable variability among the studies regarding the prevalence of driving issues in RA. Shared themes addressed included RA in association with MVAs (motor vehicle accidents), self-reported driving difficulty, inability to drive, use of driving adaptations, use of assistance by other people for transport and difficulty with general transportation.

Comment (SS): The ability to drive is an important determinant of independence, and this is particularly so in NZ, where outside the major cities, public transport is often limited or absent. Driving is often rated by RA patients as a top priority for outcomes in studies. Both upper- and lower-limb and cervical spine involvement may affect driving capacity, but studies suggest rheumatologists rarely evaluate this important function in the clinic. This is an interesting and comprehensive systematic review. A modest number of studies were identified, but they comprised a large number of patients. Most studies showed RA patients had difficulty with driving, and some used driving adaptations such as power adjustable seats, covered steering wheels, sliding doors and additional back supports. In one study, 58% mentioned that RA limited their driving ability and another 8% were completely unable to drive. Some studies showed RA patients required help and were driven by relatives, spouses or friends. Other studies showed RA patients often struggled to navigate public transport. Driving safety is very difficult to assess, as there are so many potential confounding factors. One Finnish study showed fewer MVAs in RA patients, perhaps due to this group driving less. Other studies suggested a small increase in MVAs (OR 1.6). This study provides a reminder of the importance of driving to patients with RA and the complex issues that surround driving and disability. In NZ, health practitioners have legal obligations relating to fitness to drive under transport legislation. In assessing an individual's fitness to drive, the practitioner must assess if there is a significant risk to a person's ability to drive safely and whether they are a danger to themselves or others. The presence of multiple comorbidities may result in a combined effect on a patient's ability to drive safely, and this should be borne in mind when assessing patients.

Reference: Arthritis Care Res 2021;73:489–97
Abstract

Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis

Authors: Abtahi S et al.

Summary: This UK population-based cohort study investigated the association between concomitant use of oral glucocorticoids and PPIs and the risk of osteoporotic fractures among 12,351 patients with RA aged ≥50 years, stratified according to oral glucocorticoid and PPI exposure by the most recent prescription (current use <6 months; recent use 7–12 months; past use >1 year), average daily and cumulative dose and duration of use. Incident osteoporotic fracture risk was estimated. There were 1411 osteoporotic fractures recorded. There was an increased fracture risk with concomitant current use of oral glucocorticoids and PPIs versus nonuse (adjusted hazard ratio 1.60 [95% CI 1.35, 1.89]); this was statistically different from a 1.2-fold increased fracture risk associated with oral glucocorticoid or PPI use alone. Fracture risk did not increase with higher daily dose or duration of PPI use among concomitant users.

Comment (AH): This study used data from a large primary-care research database to determine whether coprescription of glucocorticoids and PPIs influences fracture risk in people with RA. The data were stratified for PPI use in combination with oral glucocorticoids, PPIs alone and glucocorticoids alone. A large number of potentially confounding variables were considered and did not appear to explain the findings that fracture risk was increased in patients taking PPIs and glucocorticoids together, with a fully adjusted hazard ratio of 1.60 (95% CI 1.35, 1.89). Interestingly, the risk ascribed to PPIs alone was generally dose-dependent and similar to the risk for glucocorticoids alone. PPIs are known to reduce gastrointestinal calcium absorption and to increase bone resorption by osteoclasts, and there is still a possibility of unrecognised confounders, but the data seem sufficiently robust to recommend that fracture risk be considered when prescribing PPIs to older RA patients, especially if used alongside glucocorticoids.

Reference: Ann Rheum Dis 2021;80:423–31
Abstract

Efficacy of a combination of conservative therapies vs an education comparator on clinical outcomes in thumb base osteoarthritis

Authors: Deveza LA et al.

Summary: Australian patients aged ≥40 years with symptomatic and radiographical thumb-base OA were randomised to education on self-management and ergonomic principles either with (n=102; intervention group) or without (n=102; control group) a base-of-thumb splint, hand exercises and 1% diclofenac sodium gel used at the participants' discretion for 6–12 weeks; 95% of the participants completed 12 weeks of follow-up. Compared with the control group, the intervention group had a significantly greater improvement in FIHOA (Functional Index for Hand Osteoarthritis) score by week 6 (difference, –1.7 units [p=0.002]), which was maintained out to 12 weeks (–2.4 units [p<0.001]). The intervention was also associated with a nonsignificant improvement in VAS pain score by week 6 compared with controls (difference, –4.2mm [p=0.19]), with statistical significance attained at week 12 (–8.6mm [p=0.01]). All 34 nonserious adverse events occurred in the intervention group, with most being skin reactions and exercise-related pain exacerbations.

Comment (SS): OA base of thumb is the most common site for primary OA and can result in significant pain and disability, given the key role this joint plays in pinch grip and opposition. This study was a relatively large study of 204 patients randomised to either 6 weeks of combination splinting, splint, hand exercises, 1% diclofenac sodium gel and education compared with education alone. The study was well designed, with clear inclusion criteria, which included a minimum level of pain and functional impairment at baseline, and radiological evidence of thumb-base OA. There are a few criticisms to make of the study. Firstly, the functional outcome questionnaire selected, the FIHOA, contains some archaic gender-specific questions: e.g. 'for women, 'Are you able to sew?'; for men: 'Are you able to use a screwdriver?', which makes it a questionable outcome in the current millennium. Secondly, there was no dose range for the splint in terms of hours worn. Thirdly, the duration of the study was quite short for an intervention. However, the trial showed that a combination of conservative treatments for thumb-base OA conferred small-to-medium benefits on hand function that were potentially clinically meaningful, even though there was no statistical improvement in pain. This study helps to define the role for conservative therapies for base of thumb OA as well as pointing to areas for additional research, including better functional outcome assessments and perhaps a dosage-ranging study.

Reference: JAMA Intern Med 2021;181:429–38
Abstract

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