The unmet need in rheumatology: reports from the Targeted Therapies meeting 2016

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ABSTRACT

The 18th annual international Targeted Therapies meeting brought together over 100 leading scientists and clinicians from around the world in the field of rheumatology. During the meeting, breakout sessions were held consisting of 5 disease-specific groups each with 20–40 experts assigned to each group based on clinical or scientific expertise. Specific groups included: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis/spondyloarthritis, systemic lupus erythematous, and other connective tissue diseases (e.g. Sjögren's, Behçet's, others). In each group, experts were asked to identify unmet needs in 3 categorical areas: basic/translational science, clinical science and therapeutic development, and clinical care. Needs were prioritised as primary or secondary. Overall, similar primary unmet needs were identified within each disease foci. Within translational science, these included the need for better understanding the heterogeneity within each disease, such that predictive tools for therapeutic response could be developed. Within clinical science and therapeutic trials, the ability to prevent progression to disease onset in those at risk, and the ability to cure disease were identified. A further unmet need was to develop new and accessible therapeutics, as well as to conduct strategic trials of currently approved therapies. Within the clinical care realm, improved co-morbidity management and patient-centered care were identified as unmet needs. Lastly, it was strongly felt there was a need to develop a scientific infrastructure for well-characterised, longitudinal cohorts married with biobanks and mechanisms to support data-sharing. This infrastructure could facilitate many of the unmet needs identified within each disease area.

Background

The Targeted Therapies meeting has met annually for 18 years, with experts in the fields of clinical rheumatology, infectious diseases, epidemiology, and other clinical areas like immunology and molecular biology, presenting research developments in their fields. The meeting focuses on translational research and medicine and is meant to update participants on the latest developments regarding disease mechanism(s) and the development and use of targeted therapies based on understanding of disease pathophysiology, as well as stimulate collaboration between basic scientists and clinicians. Traditionally, a consensus document describing the optimal use of targeted therapies within rheumatology had been produced from this meeting (1). However, with the recent publication of recommendations from both the European Union League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) on disease management (2, 3), the Targeted Therapies consensus document appeared to add little to these guidelines. Rather the experts were asked to identify, debate and formulate a list of key unmet needs within the field of rheumatology, to help serve as a roadmap for research

Methods

Conference attendees were assigned to disease-specific breakout groups according to their expertise or interest. The groups included those for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis/spondyloarthritis (SpA), systemic lupus erythematous (SLE), and connective tissue diseases (CTD). The CTD group was asked specifically to discuss the following diseases: Sjögren's syn-

Table I. The primary and secondary unmet scientific needs within rheumatoid arthritis with regard to translational science, clinical science and therapeutic trials, and clinical care.

	Primary Unmet Need	Secondary Unmet Needs
Translational science	Understanding the role of the microbiome in disease development and modulation	Identifying sites beyond the joint (*e.g.* gut) that may be driving joint inflammation
	Development of molecular definitions of disease remission, flare, refractoriness	Development of animal models that better reflect human disease
	Identifying Biomarkers including imaging that predict or rapidly identify treatment response	
	Further development of longitudinal, clinically well-characterised cohorts with appropriate imaging, tissue and fluid samples	
Clinical science and therapeutic trials	Development of therapeutics that repair damage, including outside the joint (*e.g.* interstitial lung disease)	Development of therapeutic alternatives for analgesia
	Evaluation of existing therapies in combination	Development of non-immunosuppressive disease control
	Trials that include older patients with comorbidities that will enhance our understanding of the safety of existing therapies	Clinical Study of extreme phenotypes: those who respond very well *vs.* those who don't respond at all
	Trials evaluating the benefits of early treatment (*e.g.* change the long-term prognosis of disease)	Better understanding of secondary failure (anti-drug antibody or other mechanisms)
	The development of approaches to prevent RA (*e.g.* screening, tolerisation, vaccination)	Better understanding and categorisation of seronegative patients
		Development of infrastructure for using electronic health records in clinical research
Clinical care	Achieving cure Identifying patients who can taper their treatment Moderation of drug pricing and the improvement of access to existing and new therapies	Achieving remission in greater proportions of patients (still not more than 30%)

drome, systemic sclerosis, myositis, Behçet's disease, vasculitis, and IgG4 syndrome. In each group, experts were asked to identify unmet needs in 3 categorical areas: basic/translational science, clinical science and therapeutic development, and clinical care. Needs were categorised as primary or secondary. Each group was assigned a "leader" and "rapporteur" in charge of facilitating the discussion and communicating their findings to the conference on the last day in session. During this session, results from each group were summarised, presented, and further input was obtained from the congress. The output from each group is summarised here. No formal procedures for consensus or measures of agreement were pursued.

Results

Across all disease groups, a number of overarching themes were identified within each domain.

From a translational standpoint, it was well-recognised that additional infrastructure was necessary; specifically, in all diseases, there is need for the construction or further development of well-characterised, longitudinal, preferably inception, cohorts married with biobanks and data-sharing. Such an infrastructure would facilitate better understanding of the heterogeneity within each disease (a primary unmet need consistently stressed), the development of predictive tools for therapeutic response, and ultimately an era of personalised or phenotype-specific medicine. From a clinical science standpoint, there is continued need to diagnose early but also identify at-risk individuals to eventually prevent disease onset; as well as to develop new therapeutics, both targeted and non-targeted that are affordable and accessible to patients. Lastly, across all diseases, the need to construct strategy trials using our existing drug armamentarium was recognised, to better understand how to effectively use our currently approved therapies. Issues of improved management of co-morbidities and cross-specialty training/education and co-management were also shared as unmet needs across all diseases. Lastly, the ultimate need for new therapeutics that can cure disease was recognised.

Results of each breakout group based upon disease are summarised in tabular form (Tables I-V). For RA, specific clinical unmet need continues despite the availability of a large number of approved therapies. Additional unmet needs were articulated within each domain (Table I). Within PsA, overlap was noted with RA knowledge gaps, specifically with understanding the role of the microbiome in pathogenesis and therapy as well as strategy trials of existing therapies to address combination therapies (Table II). Within PsA, standardising measures of enthesitis and dactylitis for both trials and clinical management were unmet needs (Table III). For SLE, advances in understanding its immunopathogenesis

Table II. The primary and secondary unmet scientific needs within psoriatic arthritis with regard to translational science, clinical science and therapeutic trials, and clinical care.

	Primary Unmet Need	Secondary Unmet Needs
Translational science	Understanding how to use molecular imaging modalities to interrogate tissue pathophysiology, especially the enthesium.	Development of appropriate animal models for pathogenesis
	Better understanding the effect of genetic markers, skin and gut microbiome patterns, and metabolic syndrome on disease sub-types and their outcomes	Understanding various mechanisms of pain, including central sensitisation
	Further development of longitudinal, clinically well-characterised cohorts with appropriate imaging, tissue and fluid samples; improved data-sharing among investigators	
Clinical science and therapeutic trials	Standardisation of enthesitis and dactylitis measures	Development/validation of advanced imaging and other biomarkers including patient reported outcomes (PROs) to assess disease activity and clinical outcomes in the different clinical domains of PsA
	Reliable and feasible imaging assessment of new bone formation	
	Correlation of physical exam with advanced imaging (US, MRI)	Use of NMR spectroscopy and other advanced imaging for metabolic syndrome
		Specific interventions related to microbiome
	Understanding differential therapeutic effects on different clinical domains in PsA	
	Evaluation of combination therapies and strategic trials including the use of sequential therapies, controlled withdrawal, and the treatment of early disease	
Clinical care	Standardisation in the characterisation and measurement of PsA domains	Use of serum and other types of biomarkers for diagnosis, disease severity categorisation, and identifying structural damage
	Developing better knowledge, communication, and screening approaches (including the development of cross-specialty clinics) for rheumatologists, dermatologists, and primary care providers caring for PsA patients	
	Improved clinical attention to PsA related co-morbidities, especially metabolic syndrome	

would potentially provide opportunities for development and testing of new targeted therapies. An important focus of discussion was the need for novel steroid-sparing treatment approaches and the incorporation of socioeconomic and health disparity factors in patient management and clinical trial design. In the response measurement arena, responder analyses of data from completed clinical trials was emphasised as a valuable approach (Table IV).

For the other connective tissue diseases, the overarching needs in common across the individual diseases discussed are presented in Table V. However, given the large number of diseases included in this break-out group, only some were discussed fully with regard to unmet needs in each domain. Overall, this break-out group supported those needs also found for the other groups (Table V). Perhaps associated with the heterogeneity of the diseases, there was a great emphasis on the need to expand or create well-characterised, longitudinal patient cohorts married with biorepositories of patient specimens. Also, given the number of diseases subsumed in this break-out group, it was not surprising that a need to better define and understand disease heterogeneity was a priority. Specific priorities were identified in each domain for Sjögren's syndrome (supplementary Table I), systemic sclerosis (supplementary Table II), inflammatory myopathies (supplementary Table III) and vasculitis (supplementary Table IV).

Discussion

Participants at the 18th annual international Targeted Therapies were divided by expertise into disease-specific focus groups to identify unmet needs within the field of rheumatology.

For all groups there were several overarching perceived unmet needs. These included the need for an infrastructure necessary to study the heterogeneity within each disease and to develop predictive tools for therapeutic response. This would be best facilitated by the creation or further development of well-characterised, longitudinal patient cohorts (preferably inception cohorts) married with biorepositories of patient specimens. Within the clinical care realm a common unmet need, was improved co-morbidity management and patient-centered care Within clinical science and therapeutic development, the ability to prevent disease onset in those at risk, and the ability to cure disease were identified. Other primary unmet needs included the need for new therapeutics that are accessible, and a need for strategy trials to better understand how to use our currently approved therapies.

Within RA, the committee was quite enthusiastic about the progress that has been made in the treatment of rheumatoid arthritis. Using a "treat to target"

Table III. The primary and secondary unmet scientific needs within ankylosing spondylitis/spondyloarthritis with regard to translational science, clinical science and therapeutic trials, and clinical care.

	Primary Unmet Need	Secondary Unmet Needs
Translational science	Improved animal models: (*e.g.* TNF-dependent or ankylosing models)	Understanding immune system and mesenchymal cell interactions
	Improved understanding of disease pathogenesis including the role of B27 and other genetic markers, the development of predictive markers for disease onset and progression, better understanding of cytokine inter-relationships, and understanding of osteoclast/blast and new bone formation	Evaluating the role of microbiome in AxSpa, and linking microbiome signatures to clinical outcomes
		Better understanding of biomechanics: injury and repair, also explaining site of pathology
	Further development of longitudinal, clinically well-characterised inception cohorts with appropriate imaging, tissue and fluid samples; improved data-sharing among investigators	
Clinical science and therapeutic trials	Clinical trials including (1) TNFi + NSAIDS as inhibitors of radiographic progression, (2) TNFi plus denosumab, (3) biologic classes head to head, (4) new therapies in TNFi non-responsive patients, (5) combination therapies	For peripheral SpA (aside from PsA), improved disease phenotyping (using novel CT and MRI), generation of outcomes measures, and intervention trials
	Establishing concept and identifying at risk/pre-SpA (early *vs.* established disease) and tailoring treatments to distinct SpA phenotypes	AxSpa registry or completed targeted trials including co-morbidities and pain originating from the spinal cord or CNS
	Develop biomarker, imaging and clinical panels which have excellent PPV± NPV for disease diagnosis	
Clinical care	Improved clinical education to enhance early referral and diagnosis	Improved societal disease education and increased patient involvement in clinical research and care.
	Understanding TNFi IR: do they have active disease or concomitant conditions?	
	Development and use of precision medicine to predict response to treatment and identify patients for early biologic therapy	

strategy with the rapid dose escalation of methotrexate followed by the addition of either biologic response modifiers or small molecules has changed the course of this disease (4). The committee recognised that a significant percentage of patients, even with this strategy, still remain with moderate to high disease activity (5). There is a need for additional therapies which can be added on top of background combination therapy that will enhance the efficacy already noted without increasing the degree of immunosuppression. That said, a major challenge currently is access to care due to high cost of the biologics and new small molecules (6). This is a universal concern, independent of country of origin. Another unmet need in rheumatoid arthritis is the identification of patients who are in remission who would be candidates for dose reduction (7). Development of biomarkers or imaging programs that can identify those patients who should be able to reduce their drug dose without a risk of a flare is needed (8). Additional therapeutics that repair the damage induced in RA, new treatments to increase remission rates, new non-narcotic analgesics and also alternatives to corticosteroids were identified as an unmet need. Lastly, the role of the microbiome in RA, the development of animal models that better reflect human disease and identification of sites remote from the joint that may be driving the articular inflammatory process were also noted as areas of research interest (9, 10).

For PsA, the heterogeneous clinical domains which may variably be present in an individual patient represent a major challenge to understand in translational studies, assess in clinical trials and clinical practice, and may be variably effected by current and emerging PsA treatments (11). These domains include not only arthritis and skin disease but also enthesitis, dactylitis, spondylitis, nail disease, uveitis, and colitis (12). What are the cellular and cytokine mechanisms which underlie these varied domains; how are they similar and different (13)? There is a need for animal models of domains such as enthesitis and spondylitis, including new bone formation (syndesmophyte, enthesophyte), which can be translated to human pathophysiology. If it is difficult to investigate tissue by biopsy, e.g. for enthesitis pathology, can pathophysiologic interrogation be done by advanced imaging techniques? Evaluation of therapy combinations with different mechanisms of action to treat clinical domains with differing pathophysiology (*e.g.* bone lysis in arthritis and bone formation in spondylitis) is needed, especially if single therapy approaches work well in one domain but not in another (14). Evaluation is necessary of the currently employed

Table IV. The primary and secondary unmet scientific needs within systemic lupus erythematosus with regard to translational science, clinical science and therapeutic trials, and clinical care.

	Primary Unmet Need	Secondary Unmet Needs
Translational science	Better understanding of the role of T and B lymphocytes (and subsets), the epigenetic modification of various cell types (in connection with environmental factors), and metabolic perturbations in the pathophysiology of disease.	The development of biomarkers to identify "pre-disease" (high risk individuals) and very early disease
	Further development of longitudinal, clinically well-characterised cohorts (immunologically, genetically, and metabolically) with appropriate imaging, tissue and fluid samples; improved data-sharing among investigators	Better understanding of the natural history of disease flares
Clinical science and therapeutic trials	Further refinement of clinical response measures/index	Improved identification and targeting of the innate immune response
	Standardisation of a definition of disease remission	Improved identification and use of biomarkers within clinical practice and trials
	Clinical trials that incorporate IFN signature and emphasise responder analyses	Broaden membership of groups designing trials
	Large pragmatic trials of existing and emerging therapies Small proof of mechanism trials for emerging therapies	
Clinical care	Better characterise patient concerns (*vs*. provider concerns)	Identification of socioeconomic factors that contribute to long-standing disease
	Optimisation of steroid-sparing approaches to treatment including the development of toxicity scoring systems, the development of sustained release or organ-targeted steroid preparations, and consideration of different "phases" of steroid use.	Establish patient support groups & guides/advocates to improve adherence to medical regimen
		Better understand cognitive dysfunction associated with disease and the development of a usable instrument to quantify in clinical practice
	Improved understanding of targeting specific therapies to specific disease clinical manifestations	

Table V. The primary and secondary unmet scientific needs within other connective tissue disorders/vasculitis with regard to translational science, clinical science and therapeutic trials, and clinical care. These are overarching needs in common across individual diseases (including Sjögren's syndrome, systemic sclerosis, inflammatory myopathies, and vasculitides, including IgG4 related disease. (Individual diseases are presented in supplementary on-line appendices).

	Primary Unmet Need	Secondary Unmet Needs
Translational science	Need for better definition of the disease phenotype (heterogeneity of disease currently a problem in treatment, trial design, etc.)	
	Multi-disciplinary centres of excellence needed (led by experts to include a rheumatologist)	
Clinical science and therapeutic trials	Need for clinical trials with better defined outcome measures (clinician and patient).	Need for new targets defined by elucidation of pathophysiological processes
Clinical care	Early disease identification and treatment	Identification and management (minimisation) of co-morbidity

physical exam assessments in trials and practice to understand whether they adequately measure the disease activity of different domains and whether they correlate with advanced imaging techniques (15). Understanding of genetic and gut and skin microbiome profiles of patients with PsA is increasing (16). There is a need to utilise this profile understanding to aid with PsA diagnosis, to understand which psoriasis patients will develop PsA, and ultimately develop new therapies for PsA. Currently, there is a paucity of serum biomarkers to predict which psoriasis patients will develop PsA, to diagnose PsA, and to assess disease severity and predict long-term damage. These need to be developed using well characterised clinical registry cohorts with appropriate imaging, tissue and fluid samples. PsA patients have a proclivity to develop a number of co-morbidities, including metabolic syndrome (obesity, hypertension, hyperlipidaemia), which increase risk for early cardiovascular disease (17). There is a need for greater understanding of the impact of these co-morbidities, especially if modifiable, on disease course and outcomes through collaborative registry studies. Unlike RA, there has been a paucity of PsA studies on therapeutic strategies such

as combined or sequential therapies, controlled withdrawal, and treatment of early disease - these are needed to better inform optimal clinical care. PsA is a quintessential example of a disease which needs collaborative care between at least two different medical disciplines, rheumatology and dermatology; methods to improve communication between specialists in these disciplines and establish combined teaching clinics in training programs is needed.

In SpA, there is still a clear lack of understanding of pathogenesis (18). This includes, among others, the functional relevance of HLA-B27 and other genetic markers, as well as the relation between cytokines, inflammation and bone formation, and osteoclasts and osteoblasts. Another important aspect is the role of biomechanics in the process of injury and repair and possibly explaining the site of the pathology (19). New and better animal models (e.g. TNF-dependent and ankylosing models) as well as obtaining biological samples could facilitate further understanding of disease pathology. Tissue samples could also be linked to imaging to better understand the pathologies visualised by various imaging techniques. The 10-year goal would be to establish the pathophysiology of SPA and be able to identify persons at risk to develop SpA (*i.e.* those with 'pre-SpA'). Therapeutically, there is clear unmet need in the combination and comparison of various treatments such as TNFi plus NSAIDs with the aim to inhibit bone proliferation, the comparison of biologics head-to-head both in patients starting their first biologic and in patients who did not respond to TNFi. Strategy trials evaluating various drug orders such as BeSt for RA and/or a treat-to-target strategy such as TICORA are highly needed (20, 21). Finally, to improve clinical care, education is important to reach the goal of early referral and diagnosis. Moreover, knowing which patient subsets can be best treated with a specific biological could enhance treatment effectiveness tremendously.

Studies of SLE immunopathogenesis have contributed to impressive advances in defining important mechanisms of disease (22-25). The role of the innate immune response, particularly the type I interferon pathway; the contribution of important T cell subsets to altered immune regulation; and identification of genetic polymorphisms associated with disease were particularly noted, but significant areas of opportunity remain. Epigenetic analyses could provide a tool to understand the contribution of environmental factors to disease development and flares, and incorporating studies of metabolism was identified as an as yet untapped research opportunity (26). Study of well-phenotyped patients to relate the underlying biology of lupus to defined clinical subsets is an obvious approach that will require dedicated infrastructure and collaboration among clinicians and investigators. Notable failures of several large clinical trials in SLE have put a damper on drug development in this disease, and there is a clear need to encourage and facilitate therapeutic development (27). Analysis of responder data from completed clinical trials could lead to development of an effective responder index and guide enrolment in future clinical trials (28). A need for more flexibility in clinical trial design was emphasised, with small proof of mechanism clinical trials aiding in "go/no-go" decisions, and large pragmatic clinical trials incorporating patients from clinical practices and established cohorts. Pending development of effective new therapeutic agents, studying creative approaches to spare use of steroids was identified as a high priority unmet need. Targeting of steroid delivery to particular organs and careful consideration of timing administration of steroids were emphasised as opportunities that could reduce unwanted toxicities while optimising the acknowledged immunosuppressive function of those agents (29). Finally, the current focus on patient-reported outcomes and incorporating the outcomes most important to patients in management of disease were viewed as important approaches that could be applied to study and care of patients with SLE (30).

The CTD portion of this exercise included a number of diseases, including Sjögren's syndrome, systemic sclerosis, inflammatory myopathies and vasculitides. Definition of patient phenotypes and sub-groups using validated diagnostic/classification criteria and pathogenesis-based cytokine and cell-based functional panels were deemed important across all the CTDs. Further, long term goals included identification of patients early in their disease course, prior to organ damage, and patient subgroups where treatment of individual aspects of disease (*e.g.* organ specific manifestations) would be beneficial. The group identified the need for better tolerated and more targeted, as well as, novel treatments. In ANCA-associated vasculitis, there is need to profile serologic type before receiving any treatment – PR3 ANCA subsets should be adopted as a marker of poor prognosis, and new remission induction strategies identified for this subgroup following therapy with rituximab, anti-IL-6 agents, JAK inhibitors or even anti-GM-CSF therapies in development (31). In addition, secondary unmet needs include understanding the relationship between these auto-antibodies and pathophysiology; the patterns of disease with regard to organ distribution (32). Further work must be done to evaluate the complement pathway as both a diagnostic (e.g. more sensitive measures) and therapeutic target, as well as emphasis upon developing therapies that promote glucocorticoid discontinuation. For Behçet's disease, specifically new treatment strategies for ocular, CNS, and vascular disease are needed, as are trials of apremilast and TNF inhibitors. Outcome measures for randomised controlled trials, however, need to be better defined (33, 34). For large vessel vasculitis, IL-6 therapy needs to be confirmed as effective, outcome measures better defined, as well as evaluation of imaging (*e.g.* PET scan) in guiding therapeutic decision-making (35). Lastly, the group recognised that understanding of IgG4 related disease was in its infancy relative to the other diseases under discussion (36, 37). Basic primary unmet needs included the need to develop classification criteria, better understanding its pathogenesis, as well as the natural history of glucocorticoid

treatment. Further, outcome measures (including imaging findings) to evaluate glucocorticoid and other potential therapies in randomised controlled trials must be developed, and further evaluation of therapies directed at B cells and $CD4^+$ cytotoxic T lymphocytes are warranted.

In summary, the convening of the annual Targeted Therapies meeting afforded the possibility to discuss and articulate the major unmet needs in the field of rheumatology. A number of overarching themes were identified between individual rheumatic disease states, and despite the explosion of new therapies for RA, PsA, and other rheumatic diseases, both the continued development of new therapeutics and better understanding and targeting of existing therapies continues to represent a major unmet need for patients and rheumatologists.

Competing interests

K.L. Winthrop has received consultant honoraria or grant funds from Pfizer, UCB, Abbvie, Lilly, Roche/Genentech, and Amgen;
V. Strand has received honorariun for participation in the Targeted Therapies meeting;
D. Van der Heijde has received consultancy fees from Abbvie, Amgen, Astellas, AstraZeneca, BMS, Boeringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos Director of Imaging Rheumatology bv;
P. Mease has received research grant, consultant and speaker's fees from Abbvie, Amgen, BMS, Celgene, Crescendo, Corrona, Dermira, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Sun, UCB, and Zynerba;
M.K. Crow has served as a consultant for BMS, AstraZeneca, Medimmune, Lilly, Neovacs, Novartis, and Roche, and has received a research grant partially funded by Pfizer;
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J. Bathon has received consulting fees from Regeneron;
M. Buch has received honoraria/consultancy fees from Abbie, Bristol-Myers Squibb, AstraZeneca, Roche-Chugai, Pfizer, Sandoz, and R-Pharm, and research grants from Pfizer and Roche-Chugai;
M. Dougados has received consultancy fees and his department research grants from Abbvie, Pfizer, BMS, UCB, Merck, Lilly, and Novartis;
X. Mariette has received honoraria from BMS, GSK, LFB, Pfizer, and UCB, and research grants from Pfizer and UCB;
J.S. Smolen has received grants for his institution from Abbvie, Janssen, Lilly, MSD, Pfizer, and Roche and has provided expert advice to and/or had speaking engagements from Abbvie, Amgen, AstraZeneca, Astro, Celgene, Celtrion, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi, and UCB;
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all the other authors have declared no competing interests.

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