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REVIEW ARTICLE

Tumor necrosis factor-associated periodic syndrome in adults

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Abstract Tumor necrosis factor-associated periodic syndrome is an autoinflammatory disorder classified under hereditary periodic fever syndromes. Mutations in the tumor necrosis factor receptor contribute to tumor necrosis factor-associated periodic syndrome. Decreased shedding of receptors and increased mitochondrial reactive oxygen species production leading to elevated proinflammatory cytokines are documented. Inflammation in various organs is hallmark of tumor necrosis factor-associated periodic syndrome and manifests as spiking fever, abdominal pain, conjunctivitis and polyserositis in adults. The ongoing challenge is to diagnose the disease early in its course to prevent amyloidosis. The treatment options have evolved from use of nonsteroidal anti-inflammatory drugs and corticosteroids to targeted therapy like tumor necrosis factor receptor inhibitors and interleukin-1 blockers. The aim of this review is to give an overview of the pathogenesis, clinical features and the various treatment modalities available for tumor necrosis factor-associated periodic syndrome and aid physicians in recognizing the signs of the disease earlier.

Keywords Tumor necrosis factor-associated periodic syndrome · Hereditary periodic syndrome · Autoinflammatory disorder · IL-1 blocker

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Introduction

Tumor necrosis factor-associated periodic syndrome (TRAPS) was first described in 1982. It was initially seen in people of Irish/Scottish descent and hence known as Hibernian fever. Eventually, TRAPS was detected in other ethnic diversities including Caucasians, Japanese and Mediterranean people. It is classified under a group of autoinflammatory disorders called hereditary periodic fever syndromes [1–3]. The pattern of inheritance was earlier thought to be autosomal dominant, but there are reports of autosomal recessive TRAPS as well [4]. Other hereditary periodic fever syndrome includes familial Mediterranean fever, hyperimmunoglobulin D syndrome, Muckle–Wells syndrome and familial cold autoinflammatory syndrome [5]. Tumor necrosis factor is a cytokine produced during inflammation by macrophages and acts on its receptor on the cell membrane. Patients with TRAPS most commonly have a mutation in TNF receptor. How this mutated receptor leads to the phenotype of TRAPS is unclear. Patients with TRAPS exhibit episodes of fever, abdominal pain, periorbital edema, joint pains and migrating erythema. Long-standing TRAPS has been known to precipitate amyloidosis. Appropriate and timely treatment is paramount. Multiple therapeutic options are available including biologics. Some of the biologic medications like IL-1 and IL-6 inhibitors have shown promising results. The aim of our review is to educate clinicians about the latest advances in the pathophysiology, clinical manifestations and management of TRAPS. Initially, TRAPS was thought to be a pediatric disease, but there are increasing reports of adult onset. We have tried to draw attention to the protean presentations and phenotypic variations associated with different mutations in TRAPS.

Method

A systematic PubMed search was performed using the following keywords: "Tumor necrosis factor-associated periodic syndrome," "Hereditary periodic syndrome," "autoinflammatory disorder" and "treatment" both separately and in various combinations. Inclusion criteria included full text articles in the English language that were clinically relevant. Preference was given to the sources published within the past 15 years. Incorporated articles were focused on the genetics, pathogenesis, clinical manifestation, the diagnostic criteria and the management of tumor necrosis-associated periodic syndrome.

Pathophysiology and genetics

Tumor necrosis factor, a cytokine participating in the acute-phase response, binds to TNF receptors (TNFR1 and TNFR2) present on cell membrane [6]. *TNFR Superfamily 1A* (*TNFRSF1A)* gene codes for tumor necrosis factor receptor (TNFR). TNFR1 is a transmembrane protein with four cysteine rich residues in the extracellular domain [3]. Heterozygous missense mutations in extracellular domain of *TNFRSF1A* gene on chromosome 12p13 are responsible for TRAPS [3]. A mutational analysis study in 18 families and 176 sporadic TRAPS patients detected novel mutations in TNFRSF1A mutation-negative families [7]. Till date, more than 150 mutations have been discovered [8–10]. Over the past decade, many more mutations were identified [11, 12]. Most recently, a mutation, Thr90Pro in the TNFRSF1A has been identified in a patient with early onset TRAPS [13]. Under normal circumstances, the TNFR receptor is cleaved off and shed from the cell membrane and released into circulation. These circulating receptors compete with the receptors on the cell membrane to bind with TNF-α. There are theories that suggest TNFRSF1A mutation decreases shedding of the receptors in TRAPS and leads to uncontrolled inflammation [14, 15]. The mutant cells also increase the production of cytokines and consequently augment the inflammatory response associated with TRAPS. It is interesting to note that impaired clearance of cytokine receptor is linked to an increase in levels of TNFR1 [16].

Patients with TNFR1 mutation have significantly increased levels of reactive oxygen species (ROS). The misfolded protein in the endoplasmic reticulum is responsible for inducing stress [17, 18]. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TRAPS [19]. The levels of inflammatory mediators are elevated even in between attacks [17]. Another suggested mechanism is an apoptosis defect mediated by TNF. There is decreased activation of NF-κB in the dermal fibroblasts of people with C43S mutation in TNFRSF1A. This leads to a defect in apoptosis and increase in inflammation [20]. An association between inflammasome and TNF-α has been determined [21]. There are TNF-dependent and TNF-independent mechanisms which attribute to inflammation in TRAPS [22]. A different hypothesis suggested a relationship between microRNA and TRAPS. Lucherini et al. [23] studied this demonstrated altered levels of microRNA (miRNA) in patients with TRAPS.

Mutations which disrupt extracellular cysteine rich domains are associated with higher penetrance of phenotype and an increased risk of developing amyloidosis [14, 24, 25]. There are other mutations like R92Q which are low penetrance [26, 27]. Low-penetrance mutation of TNFRSF1A is associated with a later onset of disease [28–31]. When compared to patients with structural mutations, the patients with low-penetrance mutations have milder disease phenotype with shorter duration of symptoms, increased frequency of attacks per year and decreased progression to amyloidosis [31] (Fig. 1). Oral aphthosis and pharyngitis are more frequent in patients with low-penetrance mutation [28, 29, 32]. Patients with R92Q mutation also had a higher rate of spontaneous resolution of disease when compared to patients with structural mutations [32]. The phenotypic variations due to various mutations further add to the heterogeneous presentation of TRAPS. Patients with V173D mutation have an increased risk of cardiovascular disease, including myocardial infarction and thrombosis in arteries [33]. Two cases of patients with T611 mutation of TNFRSF1A with exacerbation of TRAPS induced by heparin have been noted [34]. Further investigation to determine the mechanism of increased inflammation with heparin in these patients needs to be determined.

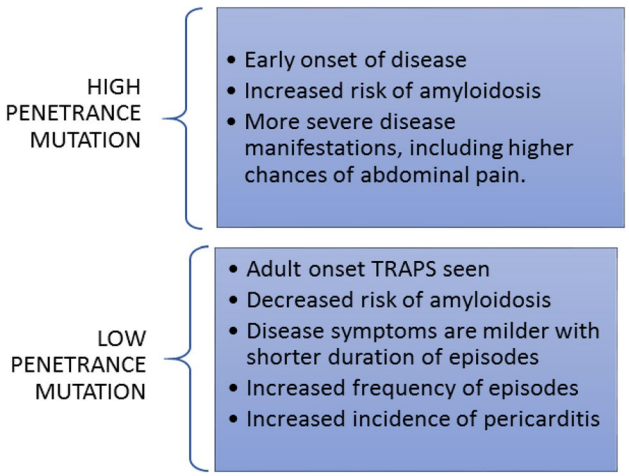

Fig. 1 Comparison between high-penetrance and low-penetrance mutations in TRAPS

Clinical presentation

The clinical presentation in TRAPS can vary considerably due to heterogeneity of phenotypes. Most patients with TRAPS have onset of disease in childhood (< 10 yrs of age); however, adult-onset TRAP is common with low-penetrance mutation [35, 36]. Recurrent inflammatory episodes for 1–3 weeks are a hallmark of the disease. An array of symptoms including fever, myalgia, abdominal pain, joint pain, skin rash and eye manifestations like conjunctivitis and uveitis is seen in TRAPS [37–45] (Table 1). The skin rash seen in TRAPS is a migrating erythema which is centrifugal in distribution [46–49]. Biopsies of the skin lesions revealed monocytic and lymphocytic infiltration surrounding blood vessels [46]. Inflammation of the peritoneum and the abdominal wall is the source of the abdominal pain. Monocytic fasciitis is one of the attributable factors for myalgia in TRAPS [50]. Incidence of lymphadenopathy and periorbital edema is more common in pediatric populations when compared to adults (Table 2). Pericarditis, pleurisy, testicular pain and inguinal hernia are also seen in some patients. Adult-onset TRAPS patients have a higher rate of pericarditis [35]. Patients with pericarditis unresponsive to colchicine or idiopathic recurrent pericarditis have a higher incidence of positive TNFRSF1A mutation [51]. Inflammation of myocardium may be rarely observed in TRAPS patients. Two case reports have described myocarditis in patients [52, 53]. Central nervous system involvement has also been reported in a few patients, but is infrequent [54–58]. Incidence of TRAPS in multiple sclerosis patients warrants further studies on the association [59]. Overlapping of autoimmune diseases like TRAPS, FMF and HIDS can lead to complex phenotypes in patients [60].

Table 2 Comparison in clinical presentation of TRAPS in pediatric and adult population

Symptom	Presentation in children	Presentation in adults
Cervical lymphadenopathy	+++	+
Abdominal pain	++++	+++
Chest pain and pleuritis	++	++++
Periorbital edema	+++	+
Pericarditis	±	++

Diagnosis

The clinical symptoms and genetic tests are the standard to diagnose the condition. Laboratory test during a flare will indicate a left shift, increased erythrocyte sedimentation rate, thrombocytosis, neutrophilia and C-reactive protein. Serum amyloid protein levels are also increased during a flare [36]. Hull et al. [25] had suggested diagnostic indicators based on clinical manifestations, response to corticosteroids, family history and ethnicity. In 2011, an autoinflammatory diseases activity index (AIDAI) was formulated and a study was conducted [61]. The index took into account many factors including abdominal pain, skin rash, nausea or vomiting, headache, chest pain, diarrhea, painful lymph nodes, overall symptoms, arthralgia/myalgia and eye manifestations (Table 3). The patient maintains a diary of his disease, and the AIDAI is calculated by the physician by scoring the variables. This was further validated by yet another study published in 2013 [62]. A score of greater than 9 indicates active disease. Recurrent pericarditis in patients with reduced response to colchicine and multiple cases of pericarditis in a family warrants genetic testing to rule out TRAPS [63, 64]. Physicians must suspect TRAPS in patients with multiple clinical symptoms suggestive of the disease and proceed with genetic testing and treatment.

Table 1 Clinical symptomatology in TRAPS

EURO TRAPS registry Lachman et al. [38] ($n = 158$)		Ozen et al. [70] ($n = 41$)[a]		José Hernández-Rodríguez et al. [39] ($n = 6$)		Ruiz-Ortiz et al. [29] TRAPS R92Q-related disease ($n = 18$)	
Fever > 38 °C	84%	Fever	44%	Fever	100%	Fever ≥ 38 °C	100%
Fever < 38 °C	36%						
Abdominal pain	70%	GI upset	41%	Abdominal pain	17%	Abdominal pain	39%
Arthralgia	64%	Arthritis excluding arthralgia	5%	Arthritis/arthralgia	67%	Arthritis/arthralgia	61%
Monoarthritis	6%						
Oligoarthritis	9.5%						
Polyarthritis	4%						
Migratory rash	18%	Rash	15%	Rash	50%	Rash	28%
Urticarial rash	25%						
Maculopapular Rash	26%						

[a]This number excludes TRAPS patients with R92Q variant

Table 3 Autoinflammatory diseases activity index (AIDAI) [61]

Autoinflammatory disease-related symptoms per day	Score
Fever > 38 °C (100.4 °F)	No (0) or yes (1)
Overall symptoms	No (0) or yes (1)
Abdominal pain	No (0) or yes (1)
Nausea/vomiting	No (0) or yes (1)
Diarrhea	No (0) or yes (1)
Headache	No (0) or yes (1)
Chest pain	No (0) or yes (1)
Painful nodes	No (0) or yes (1)
Arthralgia/myalgia	No (0) or yes (1)
Swelling of joints	No (0) or yes (1)
Eye manifestations	No (0) or yes (1)
Skin rash	No (0) or yes (1)

Score of ≥ 9 indicates active disease and < 9 indicates inactive disease

Treatment

Treatment of TRAP syndrome not only aims to decrease symptoms, but also prevent chronic inflammation leading to amyloidosis. Corticosteroids and NSAIDS are used for suppression of acute symptoms of TRAPS [40, 65]. The biologic medications used in TRAPS include TNF inhibitors, IL-1 inhibitors and IL-6 inhibitors (Table 4; Fig. 2).

Etanercept

Many studies and reports of treatment with a TNF blocker, etanercept, demonstrated decrease in disease activity and concurrent decrease in inflammatory markers [66–68]. However, a significant portion of patients discontinued the medication due to ongoing symptoms and injection site reaction [67, 69]. Similar results were seen in another retrospective study where more than 53% of the patients who discontinued treatment with etanercept cited a lack of effectiveness of the medication [70]. Use of etanercept in two patients with renal amyloidosis exhibited an improvement in nephrotic syndrome [71]. N Quillinan et al. treated patients of a family with T50M mutation in TNFRSF1A with etanercept and reported a progression to amyloidosis in 25% of the patients. 25% of the treated patients also reported incomplete response to etanercept [72].

Infliximab

Infliximab, a chimeric monoclonal antibody against TNF-α, did not show any improvement in symptoms in TRAPS and was even associated with a paradoxical reaction in some

Table 4 Comprehensive overview of drug studies in TRAPS

Drugs	Studies	Location	Results	Total number of patients
Etanercept	Quillinan et al. [72]	USA	Partial response in two patients Progression to amyloidosis in two patients	8
	Drewe et al. [71]	UK	Decrease in disease activity and reduction in corticosteroid in patients with TRAPS	7
	Bulua et al. [19]	USA	Etanercept reduced total symptom score and reduced frequency of attacks, but was associated with poor long-term compliance	15
Anakinra	Grimwood et al. [76]	France	Complete response with decreased activity score	2
	Lazaros et al. [81]	Greece	Patients with pericarditis had complete resolution of symptoms within 48 h	10
	Gattorno et al. [83]	Italy	Prompt resolution of symptoms and normalization of acute-phase reactants	5
	Camprubi et al. [80]	Spain	Patient with recurrent pericarditis had complete resolution of symptoms	1
Canakinumab	Brizi et al. [85]	Italy	Complete response with remission up to 8 months	1
	Lopalco et al.[84]	Italy	Canakinumab every 8 weeks—initial response followed by recurrence Canakinumab increased to every 4 weeks—complete response	1
	Gattorno et al. [83]	Italy	Canakinumab with alendronate led to complete resolution with normal inflammatory markers	1
	Vaitla et al. [89]	UK	Remission of symptoms	1
	Akasbi et al. [91]	Belgium	Resolution of symptoms and decreased laboratory markers	1
Infliximab	Krelenbaum M et al. [75]	Canada	TRAPS patient unresponsive to etanercept started on infliximab and dose increased to 10 mg/kg—resolution of symptom	1
	Nedjai et al. [74]	UK	Peripheral blood mononuclear cells from TRAPS patients fail to stimulate apoptotic response to infliximab	9
	Jacobelli et al. [73]	France	Infliximab was not effective in reducing TRAPS flares and was associated with paradoxical flare of disease	2

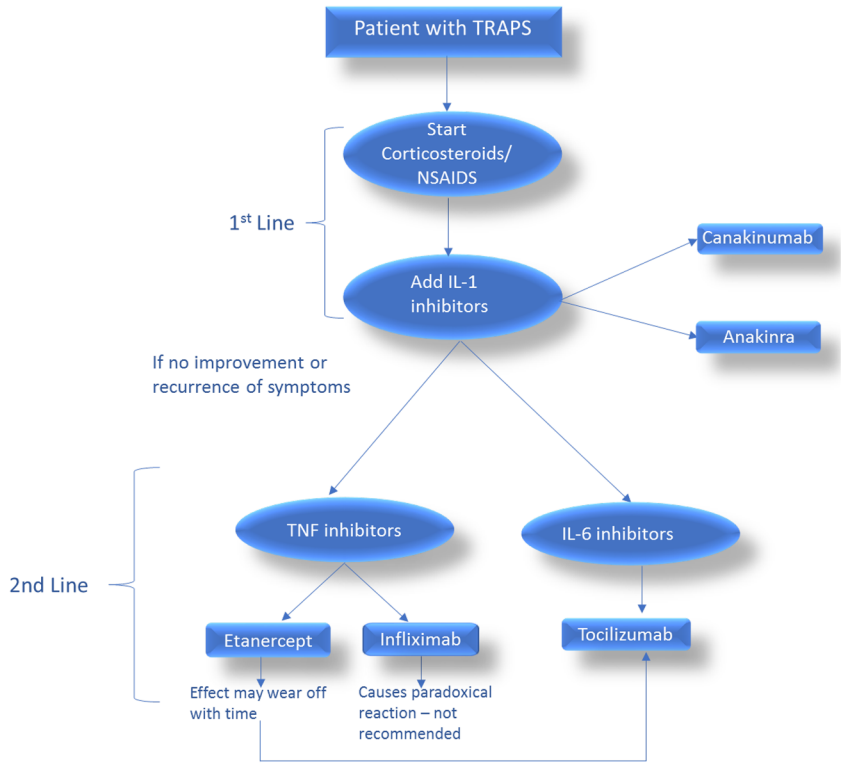

Fig. 2 Suggested therapeutic algorithm for management of TRAPS

patients [69, 73]. A study on peripheral blood mononuclear cells (PBMC) of nine patients in a family with T50M mutation in TNFR1 revealed that PBMC on exposure to infliximab secreted increased levels of proinflammatory cytokines [74]. This is very different from the usual anti-inflammatory effects of infliximab. Contradicting the above-mentioned results, one particular report states complete remission of symptoms in a patient treated with a high dose of infliximab [75].

Anakinra

Anakinra (IL-1β receptor antagonist) is a promising biologic drug for TRAPS. There are many case reports endorsing improvement in disease activity and inflammatory markers with on demand anakinra in patients with TRAPS syndrome [76, 77]. A patient with a new mutation, S59P in TNFRSF1A, responded excellently to anakinra [78]. Treatment of recurrent pericarditis with anakinra induced rapid resolution of pericarditis with negative inflammatory markers [79–81]. However, a discontinuation of the drug was associated with recurrence of symptoms in more than half of patients [81]. Treatment with anakinra in TRAPS patients led to higher clinical response when compared to anti-TNF inhibitors [70].

Canakinumab

Canakinumab is a human IgG1 monoclonal antibody which targets IL-1β, thereby preventing the attachment to the IL-1β receptor. Downregulation of gene associated with TRAPS (TNFRSF1A) is one of the mechanisms by which canakinumab decreases the symptoms in the disease [82]. Canakinumab is very effective at controlling symptoms of TRAPS and inducing rapid remission of disease. Withdrawal of the drug was associated with a relapse in the disease [83, 84]. In a case report, a TRAPS patient with local reaction to etanercept and anakinra was successfully treated with canakinumab. Short-term remission of clinical symptoms along with normalization of erythrocyte sedimentation rate, C-reactive protein and serum amyloid A levels was noted. The patient was followed up to 8 months after the treatment and did not experience any acute attacks [85]. A randomized control trial of 46 patients with TRAPS showed complete response in 45.5% of the patients receiving canakinumab [86]. It is approved for treatment of TRAPS, CAPS, HIDS, FMF and sJIA. The recommended dosage for TRAPS is 2 mg/kg every 4 weeks for patients with body weight less than 40 kg and 150 mg every 4 weeks for patients with body weight of more than 40 kg. The canakinumab injections are administered every 4 weeks, thereby reducing the discomfort of daily dosing and increasing patient compliance. The common adverse effects associated with the drug include local injection site reactions and nasopharyngitis. Patients on canakinumab are at increased risk of serious infections and should remain vigilant and report any infections to their doctor. Overall, the safety and efficacy of the drug were proved [86].

Tocilizumab

IL-6 is a cytokine secreted by T lymphocytes that regulates acute-phase reactions inducing reactants like fibrinogen, serum amyloid A (SAA), α-1 antichymotrypsin, C-reactive protein, etc. It also mediates process of maturation of B cells into antigen-producing cells [87]. IL-6 levels are raised in patients with TRAPS. Tocilizumab is a humanized monoclonal antibody which acts by binding to the IL-6 receptors. Tocilizumab was initially used for rheumatoid arthritis (RA) and systemic onset juvenile idiopathic arthritis (sJIA). Currently, it is proved to be efficacious in many autoimmune disorders [88]. Vaitla et al. [89] successfully used tocilizumab in a TRAPS patient for the first time with resolution of symptoms. The patient also reported decrease in pain and stiffness associated with TRAPS. IL-6 blockers have proved effective in patients whose disease was not controlled with TNF blockers [90–92]. It is important to be vigilant regarding thrombocytopenia which is a known side effect of tocilizumab.

Complications

Long-term disease may lead to reactive amyloidosis due to deposition of SSA fibrils in organs. SSA is an acute-phase reactant which is usually degraded by macrophages and lysosomes. If the degradation process is hindered, the SSA may be deposited in extracellular spaces of organs and result in amyloidosis [93, 94]. Most commonly affected organs are kidneys, liver and spleen [95]. Risk of amyloidosis is increased in patients with positive family history and high-penetrance phenotype. Renal amyloidosis presents as nephrotic syndrome with proteinuria [95]. Renal transplantation is associated with long-term survival of allograft. In many instances, the patients did develop amyloidosis in the transplanted kidney [96]. Glomerulonephritis not associated with amyloidosis may also be a possible manifestation of TRAPS [97]. An overwhelming inflammation due to cytotoxic T cells and macrophages is one of the complications of TRAPS. This is called macrophage activation syndrome (MAS), and it is critical to treat. The first incidence of MAS in TRAPS was reported in 2013. Fever, hyperferritinemia, splenomegaly and pancytopenia are some of the features of MAS. Diagnosis can be made based on clinical presentation and laboratory levels. Bone marrow biopsy revealing histiocytosis can determine the definitive diagnosis. Early and prompt treatment would reduce the morbidity and mortality associated with MAS [98, 99].

Discussion

TRAPS is an autoinflammatory disorder that is relatively rare. The pathophysiology of the disease, despite significant advances in understanding the genetic background, is not completely understood, and further studies in the future will assist us in understanding the disease better and formulating targeted treatments. It is crucial that physicians recognize the symptoms of TRAPS, by maintaining a high index of suspicion, and diagnose it early or refer to specialized centers. TRAPS should be considered in any patient with recurrent episodes of fever, abdominal pain, joint pain, muscle pain and rash for more than 6 months. The treatment of TRAPS with biologics may help in preventing amyloidosis.

Due to high rate of discontinuation of therapy, TNF-α blockers are not preferred as monotherapy in patients with TRAP. In patients with renal amyloidosis, etanercept was associated with reduced nephrotic syndrome and disease progression. Patients demonstrated a good response to IL-1 and IL-6 blockers. Canakinumab has shown clinically significant efficacy and acceptable safety in controlled trials and is currently FDA-approved for the treatment of TRAPS. Anakinra has shown promising results as induction and maintenance treatment. However, these promising medications also have limitations. There is still a lack of long-term data, both for efficacy and safety. Adverse reactions have been reported, even with the currently available studies. Injection site reaction, increased infection risk and inadequate response to the medication are some of the drawbacks of treatment with the soluble TNF receptor etanercept. One of the major concerns with the chimeric anti-TNF monoclonal antibody infliximab was a paradoxical flare of the disease. IL-1 inhibitors like anakinra and canakinumab have a favorable side effect profile, although increased susceptibility to infection and relapse after discontinuation of the drug has been reported. Injection site reaction and upper respiratory tract infection with canakinumab are significant. Thrombocytopenia has been reported in TRAPS patients treated with the IL-6 inhibitor tocilizumab. The high costs associated with biologic treatment that restrict patients' access to targeted treatments may further add to the limitations in the management of the disease. There is an unmet need for further research to determine long-term effects of these medications, their effectiveness in TRAPS and its complications. The fact that there are different genotypes associated with different clinical presentations and, likely, different response to treatment further complicates this effort.

Compliance with ethical standards

Conflict of interest Sharika Gopakumar Menon and Petros Efthimiou declare that they have no conflict of interest.

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