Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 1 September 2016, doi:10.4414/smw.2016.14341

Cite this as: Swiss Med Wkly. 2016;146:w14341

Guidelines for the treatment of gout: a Swiss perspective

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Summary

Gout is a common condition and its management is suboptimal. A number of guidelines on the management of gout have been published in the last decade by professional societies with the aim of informing the physician of the recommended therapeutic strategies and the treatment options. We have tried to synthesize the current recommendations and to highlight some challenges that still need to be resolved in clinical practice in Switzerland.

Key words: *gout; treatment; guidelines; hyperuricaemia*

Introduction

Gout is a urate crystal deposition disease due to underlying hyperuricaemia, and both are common conditions that have seen a marked increase in both incidence and prevalence in the last 30 years. No Swiss data are available to document its extent in Switzerland, but based on data from the UK [1] and Germany [2], it would be safe to assume that gout affects between 1% and 2% of the adult population, and is probably the most frequent cause of inflammatory arthritis in adult males [3]. A temporal trend of increasing prevalence of gout over the last 15 years was observed in the UK data, in particular affecting the elderly, and this is in agreement with our clinical experience in Lausanne.

The treatment of gout rests on two primary objectives – the relief of pain of the acute gouty attack and the reduction of serum urate to a level that prevents further urate crystal deposition. In most cases, the causes of hyperuricaemia and gout are unknown and long-term treatment with urate lowering therapy (ULT) aims to bring the serum urate level to below a target level of 360 µmol/l, a threshold that favours crystal dissolution. Dietary modifications and avoidance of drugs that provoke hyperuricaemia are indispensable adjuncts to pharmacological therapy in patients with established gout, but are generally insufficient by themselves [4]. No controlled trials of dietary therapy in gout have been performed to date.

Our current challenges in the management of gout are: the limited number of effective medical therapies that are available to our patients, particularly in Switzerland; the generally high level of attrition of patients on long term ULT; and the rational prescription of ULT in patients who often have significant cardiovascular and renal comorbidities. In fact, the presence of comorbidities is one of the major barriers to effective treatment of both acute attacks of gout and hyperuricaemia.

Recent advances in the understanding of the pathophysiology of gout [5, 6] and the development of new drugs have led to renewed interest in this old disease. It is widely recognised that gout is poorly treated in general, and there are multiple obstacles to care, in particular in adherence to therapy [7, 8]. One way to overcome some of these barriers is the development of guidelines to help the clinician to manage gout more effectively [9, 10]. In Switzerland, no local guidelines exist and clinicians frequently refer to international guidelines from other countries. In this review, we have analysed and compared the current international guidelines for the management of gout and identified points that are common to the published guidelines, as well as differences. We hope this information will be useful to Swiss clinicians and inform their choice of therapy.

Methods

Recently published guidelines on the management of gout and hyperuricaemia formed the starting point of our analyses. These include the guidelines published by European League against Rheumatism [9], the American College of Rheumatology (ACR) [10, 11], the British Society of Rheumatology [12] and the Japanese Society of Gout and Nucleic Acid Metabolism [13], as well as an international expert group called the 3e initiative [14]. All the published guidelines used an evidence-based medicine approach to produce their recommendations. In the event of differences in the guidelines' recommendations, we performed a literature review of publications that are cited in PUBMED from 1999 to 2015, and analysed the data according to the criteria of the Centre for Evidence-based Medicine (http://www.cebm.net). We have listed the different treatments used, their usual dose and dose adaptation when indicated (e.g., in the presence of renal impairment).

Who to treat

All guidelines recommend initiating ULT in cases of established gout (i.e. presence of tophi or evidence of multiple joint involvement and recurrent attacks, joint damage with typical erosions). The diagnosis of gout can be based on clinical criteria, but the gold standard remains the identification of crystals in the joint fluid by microscopy. Recent studies have identified clinical features that may help the clinician to reach a diagnosis in the absence of microscopy, but their sensitivity and specificity are inferior to crystal identification [15, 16].

There is no consensus on whether pharmacotherapy should be started after the first attack of gout in all patients, but if a patient has had more than two attacks, it is usually recommended. In patients who have had only one attack, but who also have coexisting medical problems such as chronic kidney disease (CKD) >stage 2 or a history of nephrolithiasis, initiation of ULT is generally recommended. All the guidelines, the Japanese guideline being the exception, currently do not recommend treatment of asymptomatic hyperuricaemia. In Japan, ULT is recommended in asymptomatic hyperuricaemia (serum level >8 mg/dl [480 µmol/l]) if coexisting conditions such as renal impairment, nephrolithiasis, hypertension, ischaemic heart disease, diabetes or the metabolic syndrome are present. There is evidence from clinical trials that ULT (in particular with allopurinol) may have beneficial effects in patients with heart failure and hypertension, and not necessarily all have hyperuricaemia; but these studies are in the main short-term and of small sample size [17, 18].

Treatment of acute gout and flare prophylaxis

General principles

All recommendations agree on the importance of prompt pharmacological treatment of an acute gout attack, and treatment should be started upon the first signs and symptoms of an acute attack (ideally within the first 24 hours). Nonpharmacological treatments, such as topical ice-packs, may be useful adjuncts but by themselves are usually insufficient to treat an acute attack.

Treatment of an acute attack

The most commonly used drugs are oral nonsteroidal anti-inflammatory drugs (NSAIDs), oral colchicine and corticosteroids. There is good evidence of efficacy for all three when used as monotherapy [19–22]. Table 1 summarises the agents currently used to treat an acute attack.

Nonsteroidal anti-inflammatory drugs

As mentioned above, NSAIDs are considered the first-line treatment for management of an acute gout attack. All recommendations agree that fast-acting oral NSAIDs at maximum doses should be prescribed as soon as an acute attack occurs, and should be continued until complete resolution of the attack. Six NSAIDs (naproxen, indomethacin, tenoxicam, celecoxib, etoricoxib and etodolac) have been studied in a randomised controlled trial setting for the treatment of gout [19, 20, 22–25]. Only one of them (tenoxicam) was compared with placebo [26].

The recommended treatment dosages are:

1. Naproxen 500 mg twice daily.
2. Indomethacin 50 mg three times daily
3 Tenoxicam 40 mg once daily
5. Etoricoxib 120 mg once daily

NSAIDs should not be used when known contraindications (allergies, bleeding disorders, CKD, etc.) are present.

Colchicine

Colchicine is an historical treatment for gout, but its use has had a poor reputation in Switzerland because of side effects, some of which were fatal. This was probably a result of the use of higher doses of colchicine in older recommendations. Current evidence shows that lower starting doses are just as effective and have fewer side effects, the most common being diarrhoea. For colchicine, a starting dose of 1 or 1.2 mg is recommended (dosing depends on the formulation of colchine, which is different in the USA vs EU countries), followed by 0.5 or 0.6 mg in the next 2–3 hours on the first day, and then a daily dose of up to 1.5 mg daily until complete resolution of symptoms [10]. The pharmacokinetics of colchicine in the context of renal impairment have not been extensively studied, but the drug is eliminated primarily by the kidney, so dosage should be reduced in patients with CKD, and patients with severe CKD should be monitored closely in case of side effects [27].

Corticosteroids

Corticosteroids are often used when an NSAID or colchicine are contraindicated, such as in patients who have severe renal impairment, but have also been compared directly with indomethacin in a randomised controlled trial and found to be equally effective and less likely to provoke gastrointestinal side effects [22]. The recommended oral dose, according to the ACR guidelines, is around 0.5 mg/kg per day. This dose can either be maintained for 5–10 days or given for 2–5 days, followed by gradual tapering over 7–10 days.

Alternative methods of administration of corticosteroids include intramuscular injection or intra-articular injection, which are also effective and are recommended in the guidelines. In the case of intramuscular corticosteroids, triamcinolone acetate 40–60 mg has been shown to be effective [28] and in clinical practice methylprednisolone 40–80 mg is often used, but has not been studied specifically. The dose of intra-articular corticosteroids depends on the size of the joint, but typically a knee or shoulder joint can be injected with 40 mg of methylprednisone [29]. This approach is particularly suitable for a patient presenting with one or two affected joints, but is obviously not feasible in patients with gouty polyarthritis.

Interleukin-1 inhibitors

Interleukin-1beta (IL-1β) has been shown to be a key cytokine mediating gouty inflammation and IL-1 inhibitors have been shown to be effective in randomised controlled trials and in case series. The ACR guidelines include IL-1 inhibitors as “off-label therapy”, which can be considered in patients who do not respond adequately to conventional

therapy or who have contraindications to these drugs (NSAIDs, colchicine and steroids). Two IL-1 inhibitors are currently licensed for clinical use (anakinra and canakinumab). Neither is registered for the treatment of gout in Switzerland, although canakinumab has obtained approval from European Medicines Agency for the treatment of gout. The use of anakinra is typically of short duration; it is given at a dose of 100 mg subcutaneously daily for three consecutive days. In the case of canakinumab, a 150-mg dose subcutaneously has been found to be rapidly effective in randomised controlled trials of acute gout, and also compared favourably to triamcinolone in terms of pain relief and protection from subsequent flares [30]. Both agents may help the patient who has persistent gouty arthritis and who is refractory to standard treatments, but their safety profiles and risk/benefit ratios require further assessment [31].

Pharmacological prophylaxis of acute attacks

Acute flares are frequently precipitated by the introduction of ULT. The flare rate is highest during the first 3 months of starting ULT, but the increase can persist for up to 6 months, hence the recommendation to give prophylaxis against gout flares for up to 6 months. In principle, the same medications used in treating acute attacks are given, and treatment should be tailored to the individual patient according to medical history and comedications. It is probably not necessary to start prophylaxis before ULT, but there is some variation in clinical practice based on experience.

Colchicine

Colchicine is probably the drug most frequently recommended for prophylaxis, on the basis of data from numerous randomised controlled trials of ULT. The daily dose is 0.5 to 1 mg daily and the dose should be adjusted in the presence of renal impairment. Recent randomised controlled trials of ULTs have included colchicine as prophylaxis on starting therapy. A significant flare rate was observed when prophylaxis was only given for 2 months, hence the recommendation for a 6-month duration of prophylaxis [32]. In patients with non-tophaceous gout, the ACR guidelines have also recommended prophylaxis to be maintained for 3 months after the patient has achieved his target urate level. Other guidelines found reasonable evidence to support the use of low dose colchicine for prophylaxis, but without suggesting a dosing regimen.

Nonsteroidal anti-inflammatory drugs

There is a small body of evidence for the use of NSAIDs in prophylaxis. Guidelines generally suggest use of moderate-to-low doses of an NSAID (such as naproxen 250 mg twice daily). The effective doses of other NSAIDs have not been reported in the literature, but it is likely that they are equally effective. Obviously, care should be taken when prescribing NSAIDs in the context of known contraindications (such as CKD or bleeding disorders).

Treatment of hyperuricaemia and established gout with urate lowering therapies

Reducing the serum urate level in order to prevent crystal deposition and accumulation is the cornerstone of our therapeutic approach in gout. The patient population that requires treatment has already been discussed, but it is relevant to point out that some clinicians feel that even patients who have had only one proven attack of gout could benefit from ULT. The aim of ULT is to bring the urate level to less than 360 µmol/l (6 mg/dl), which is generally accepted to be the solubility threshold of urate in blood. All guidelines recognise that this is the minimum target we should aim for in our patients, and in some clinical situations, such as tophaceous gout, the target should be even

Table 1: Pharmacological approaches to the treatment of acute gout.

	Usual daily dose	Duration of treatment	In cases of renal failure	Supporting literature
NSAIDS	Naproxen 500 mg b.d. Indomethacin 50 mg b.d. Celecoxib 800 mg once, then 400 mg on day 1, then 400 mg b.d. Tenoxicam 40 mg q.d. Etoricoxib 120 mg q.d.	Until attack completely resolves	Not recommended	Janssens et al. [19] Schumacher et al. [20] Schumacher et al. [23] Garcia de la Torre et al. [24] Schumacher et al. [20]
Colchicine	0.5–1.5 mg per day.	2 or 3 days after resolution of clinical signs	Dose reduction in patients with severe CKD [23]	Ahern et al. [21]
Oral glucocorticoids	0.5 mg/kg per day. Prednisone 30 mg day one, then taper over 7–10 days.	Up to 10 days, followed by discontinuation	Not contraindicated	Man et al. [22]
Intra-articular glucocorticoids	Triamcinolone: Large joint 40 mg. Medium joint 30 mg. Small joint 10 mg (1).		Not contraindicated	Fernandez et al. [29]
Parenteral glucocorticoids	IM: Triamcinolone 60 mg (2), followed by oral prednisone. IV: Methylprednisone 20 mg. Stepwise dose reduction by half when improvement begins.	IM: repeat at 48 h if symptoms persist. IV: 5 days.	Not contraindicated	IM: ACR panel recommendation. IV: Treatment of acute gout. Becker et al. Up-to-date article
Anti IL-1	Anakinra: 100 mg SC Canakinumab: 150 mg	Anakinra: For 3 days.	Not known	Dumusc et al. [31] Schlesinger et al. [30]

ACR = American College of Rheumatology; b.d. = twice daily; CKD = chronic kidney disease; IL-1 = interleukin-1; IM = intramuscularly; IV = intravenously; NSAIDS = nonsteroidal anti-inflammatory drugs; q.d. = once daily; SC = subcutaneously

lower (e.g., below 300 µmol/l). As mentioned previously, there are multiple lines of evidence that hyperuricaemia may contribute to a deterioration of renal and cardiovascular function, but all current guidelines, except the Japanese guideline, do not recommended treatment of asymptomatic hyperuricaemia as there is a lack of data from long-term, large scale research trials in this sector.

The first step in the management of all cases of gout is to ensure that the patient is informed of nonpharmacological approaches (diet and lifestyle recommendations), the avoidance of substances (including drugs) that elevate serum urate and the importance of long-term adherence to treatment of the condition. Diuretics (thiazide and loop) are commonly prescribed drugs for heart failure that contribute to hyperuricaemia, and if possible their dose should be reduced. These general measures are summarised in table 2.

In most cases, a nonpharmacological approach is insufficient to halt the evolution of gouty arthritis or to reduce the serum urate to the target level. ULT with either a xanthine oxidase inhibitor or with a uricosuric agent is effective in lowering serum urate, although there is considerable individual variation in the response to a specific drug as well as in tolerability of medication. In general, monotherapy is the approach of choice, although combining a xanthine oxidase inhibitor with a uricosuric has also been successful. The treatments and their clinical applications are summarised in table 3.

Xanthine oxidase inhibitors

All guidelines recommend starting ULT with a xanthine oxidase inhibitor. The most commonly prescribed is allopurinol, as it is widely available. The dose of allopurinol should be increased progressively, starting at a dose of 100 mg/day and increased every 2–5 weeks by 100 mg/day in order to achieve the target serum urate level [1, 2]. Many physicians wrongly believe that the maximum daily dose is 300 mg, and do not escalate allopurinol above this level. However, less than 50% of patients achieve a target urate level of 360 µmol/l with 300 mg daily [32]. The maximum recommended dose is 900 mg/day in patients without renal impairment. The concern with higher doses, the potential association with severe side effects (allopurinol hypersensitivity syndrome, Stevens-Johnson syndrome), has led to adoption of guidelines recommending dose reduction in patients with CKD [33]. Some recent data showed that careful and gradual dose increases above 300 mg are not associated with major side effects [34] and the ACR guidelines support this approach, as long as there is close clinical surveillance. The ACR guidelines also recommend testing for the presence of HLA-B*5801 in patients who may have a higher risk of developing allopurinol hypersensitivity syndrome (e.g., Koreans, Han Chinese and Thai) as in these

Table 2: General measures in the management of hyperuricaemia (based on American College of Rheumatology recommendations [11]).

Drugs	Avoid drugs or substitute drugs that cause hyperuricaemia, e.g. thiazides, calcineurin inhibitors
Dietary modifications	Avoid high purine content foods, sugary (high fructose content) drinks
Alcohol consumption	Limit consumption of alcohol, in particular beer and spirits
General health measures	Increase in physical activity, weight reduction

Table 3: Summary of commonly used urate lowering therapies and their usage.

	Initiation	Management therapy	Usual dosage	Maximum dosage	In renal failure	Haemodialysis	Contraindications
Allopurinol (Zyloric®)	100 mg/day	Increase by 100 mg/day every 2–5 weeks.	300 mg/day	900 mg/day	Starting dosage: 50 mg/day (in stage 4 or worse CKD). Dose can be raised above 300 mg/day with adequate patient education + monitoring.	100 mg alternate days given after dialysis. With daily dialysis: an additional 50% of the dose may be required postdialysis.	Hypersensitivity syndrome. Test for HLA-B*5801 in patients at higher risk of allopurinol hypersensitivity syndrome Concomitant use of azathioprine or mercaptopurine
Febuxostat (Adenuric®)	40 mg/day	Increase to 80 mg/day after 2 weeks if the target is not reached.	80 mg/day	120 mg/day	No adjustment. More effective at 80 mg/day	Not been studied	Concomitant use of azathioprine or mercaptopurine
Benzbromarone (Desuric®)	100 mg/day	Increase by 50 mg/day increments until the serum urate level is in the target	100 mg/day	200 mg/day	No significant effect (in combination) with CrCl <30 ml/min.	Probably not effective	Hepatic disease, past history of nephrolithiasis
Probenecid (Santuril®)	250 mg 2×/day for 1 week then 500 mg 2×/day	Increase dosage by 500 mg every 4 weeks	500 mg 2×/day	1000 mg 2×/day	Not effective with a CrCl <30 ml/min. Not recommended first-line therapy with CrCl <50 ml/min.	No recommendations	Past history of nephrolithiasis
Pegloticase	8 mg 1×/2 weeks	Always the same dosage. No consensus on the appropriate duration of therapy.	8 mg 1×/2 weeks	8 mg 1×/2 weeks	No adjustment.	No recommendations	Glucose-6-phosphate dehydrogenase deficiency

CKD = chronic kidney disease; CrCl = creatinine clearance

populations the presence of HLA-B*5801 significantly increased the odds ratio of developing a severe reaction [35]. Febuxostat is a newer xanthine oxidase inhibitor that is, unfortunately, not yet available in Switzerland. Many studies have compared its efficacy with that of allopurinol in lowering urate to the target of <360 µmol/l. Febuxostat 40 mg/day is equivalent in efficacy to allopurinol 300 mg/day in lowering urate levels and it is more normally prescribed at a dose of 80–120 mg/day [36]. An advantage of febuxostat is that no dose adjustment is necessary with CKD, and it is an alternative to allopurinol in patients with CKD and patients who are hypersensitive to or show intolerance of allopurinol. Febuxostat is recommended as first-line therapy together with allopurinol in the ACR guidelines [11].

Uricosurics

As second-line therapy, all guidelines recommend a uricosuric. This treatment increases the renal excretion of urate and is, therefore, not recommended for patients with a history of renal lithiasis. In Switzerland, probenecid (Santuril®) is the main choice; benzbromarone (Desuric®) is a more effective uricosuric, but it is available only in hospitals and is reserved for patients who did not tolerate allopurinol. Probenecid can be introduced as monotherapy or in combination with a xanthine oxidase inhibitor. A study on the efficacy and tolerability of probenecid demonstrated that the target serum urate level is achieved more frequently when it is combined with allopurinol than when it is given as monotherapy [37]. Benzbromarone is more potent that probenecid in reducing serum urate [38] and has been studied as monotherapy or in combination with a xanthine oxidase inhibitor. The usual daily dose is between 100 mg and 200 mg. Because of reports of acute liver injury, it is important to check liver function before and during treatment [39].

Pegloticase

Pegloticase is a pegylated form of uricase that is available in the USA (Krystexxa®), but not in Switzerland, for the treatment of gout that has not responded to other standard therapies. It is an intravenous treatment given once every 2 weeks and has been shown to be extremely effective, compared with placebo, in achieving the target serum urate level [36]. The treatment is associated with potential allergic reactions to the drug. There is no consensus on the appropriate duration of therapy [11].

Urate lowering therapy and chronic kidney disease

Treating patients with renal impairment is a common scenario in gout and requires particular attention, as there is a fear that this will result in adverse drug reactions. The majority of publications about management of gout in CKD included patients with a creatinine clearance >30 ml/min, and there is little data on how to use ULTs in patients with stage 4 CKD or maintained on dialysis [40]. Because of the concern about adverse reactions, many patients with CKD do not get to the therapeutic target level of urate with their treatment, and some are not treated at all.

The ACR guidelines on the use of allopurinol in patients with CKD differ from the information given in the manufacturer's prescribing information and the dose adjustment proposed by Hande [33]. The ACR guidelines recommend starting allopurinol at a dose of 50 mg/day in stage 4 CKD; the dosage can be raised gradually (by 50-mg increments) to doses that may exceed 300 mg/day, but it is important that this is accompanied by patient education and regular monitoring.

For febuxostat there is no dose adjustment in mild-to-moderate CKD. There is little data on its safety in stage 4 CKD or in the dialysis setting [41]. Febuxostat 80 mg/day was shown to more effective than 40 mg/day in achieving target serum urate levels in cases of CKD with creatinine clearance between 30 and 90 ml/min [42].

In the manufacturer's prescribing information, probenecid is not indicated in renal failure and in the ACR guidelines it is not recommended as monotherapy in patients with a creatinine clearance <50 ml/min.

The use of benzbromarone in CKD has been investigated in only a limited number of studies. Perez-Ruiz concluded that benzbromarone is more effective than allopurinol (the dose of which was adjusted according to creatinine clearance) in patients with moderate CKD (mean creatinine clearance 54 ml/min) [43]. Benzbromarone in combination with allopurinol had a significant effect of serum urate level [40]. Finally, in a small Japanese study, patients with CKD stage 3 or greater responded to benzbromarone without worsening of renal function. These results are encouraging, but larger studies are required to confirm the safety of benzbromarone in CKD.

For patients on haemodialysis, recommendations are sparse. With allopurinol, prescription of 100 mg on alternate days, given after dialysis, has been suggested. In the case of daily dialysis, an additional 50% of the dose may be required after dialysis [44]. In the American Index of Drugs (Micromedex), it was reported that benzbromarone is ineffective in patients on haemodialysis. For febuxostat and probenecid there are no recommendations.

Discussion

The aim of this review was to bring together the latest international recommendations on the management and treatment of gout, and to provide the Swiss physician with an update on what these guidelines recommend. The two arms of gout therapy are (a) the relief of symptoms during an acute attack, and (b) the reduction of urate levels to prevent crystal formation and deposition. A common concept of all recommendations is the need to treat to a specific target urate level (treat-to-target) with the available range of pharmacological agents, and to maintain urate levels below this target in order to obtain remission. This target may have to be adapted to the particular clinical situation (e.g., in tophaceous gout or patients who present frequent attacks of polyarthritis) and requires thorough patient education to ensure adherence. The need to give prophylaxis during ULT is emphasised, as this will improve adherence to ULT, which is usually life-long.

Although we have effective medications, their current number is limited and we need to use the available drugs correctly to achieve disease remission. One major problem that is poorly covered in all the current guidelines is the

choice of treatment in patients who have comorbid conditions such as CKD, hypertension, diabetes or liver disease. These comorbidities are extremely common in the gout population [45] and pose barriers to the use of particular drugs. A common problem is CKD, and there is currently insufficient data to recommend specific drugs that are more effective or safer in this situation. However, both for treating acute flares and for long term ULT therapy, the physician has a number of alternatives, already mentioned above, that may pose less of a risk to renal function and less risk of drug side effects. Future research will need to focus more on this population to ensure that the recommendations are based on solid evidence and not just expert opinion.

In Switzerland, the physician treating gout faces an additional challenge because of the limited availability of drugs that are licensed and commonly used in neighbouring countries. Colchicine is not included in the list of pharmaceutical specialities (Liste des Specialités Suisse), but is recognised in the list of medications with tariff (Liste des médicaments avec tarif). Febuxostat is not yet registered in Switzerland, but is the only alternative xanthine oxidase inhibitor for patients who do not tolerate allopurinol. Benzbromarone was withdrawn from the Swiss market in 2003 and is not authorised by Swissmedic (the Swiss Agency for Therapeutic Products), so its prescription is the entire responsibility of the prescribing physician. These examples illustrate that treating gout is not always a simple affair in Switzerland, and usually entails extra administrative work in dealing with insurers.

Finally, for a disease that is so common, the available number of treatments is not great (two xanthine oxidase inhibitors, two uricosurics). Hopefully, in the future, new medications will be discovered that will increase our therapeutic armamentarium and provide alternatives to treat this very curable disease.

Disclosure statement: AS has received consultancy fees from AstraZeneca and SOBI on gout study design and speaker fees from Menarini.

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