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Uricémie à l'objectif : le challenge des experts de la goutte. Étude rétrospective sur 3 centres experts en France

Etude Urate-Challenge

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Avertissement

La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Sigles

360-target	*360µmol/L (6mg/dL) uricemia target,* objectif d'uricémie inférieur à 360µmol/L (6mg/dL)
ACP	*American College of Physicians*, Collège Américain de Médecine Générale
ACR	*American College of Rhumatology*, Collège Américain de Rhumatologie
AIC	*Glycosylated hemoglobin*, hémoglobine glyquée
AIC	*Akaike information criterion*
ALLO	Allopurinol
APHP	Assistance Publique - Hôpitaux de Paris
ATU	Autorisation temporaire d'utilisation
BMI	*Body mass index*, indice de masse corporelle
BSR	*British Society of Rheumatology, Société Anglaise de Rhumatologie*
CRP	*C-reactive protein*, protéine C-réative
DECT	*Dual Energy Computed Tomogragraphy*, scanner double énergie
DTT	*Difficult-to-treat gout*
eGFR, DFGe	*Estimated gGlomerular filtration rate*, débit de filtration glomérulaire estimé
EMA	*European Medicines Agency*, Agence Européenne du Médicament
EULAR	*European League Against Rheumatism*, Ligue Européenne Contre le Rhumatisme
FBX	Febuxostat
GHICL	Groupement des Hôpitaux de l'Institut Catholique de Lille
HTA	Hypertension artérielle
IQR	*Interquartile range*, intervalle interquartile
M0	*Month 0*, consultation initiale
M12	*Month 12*, consultation de suivi à 12 mois

M24	*Month 24*, consultation de suivi à 24 mois
M6	*Month 6*, consultation de suivi à 6 mois
MA, AMM	*Marketing authorization*, autorisation de mise sur le marché
NSAID, AINS	*Non-steroidal anti-inflammatory drug*, anti-inflammatoires non stéroïdiens
PAOD	*Peripheral arterial occlusive disease*, arthériopathie oblitérante des membres inférieurs
PIH	Prescription initiale hospitalière
PTE, ETP	*Patient therapeutic education*, Education thérapeutique des patients
RNIPH	*Research non-involving the human person*, recherche n'impliquant pas la personne humaine
SD	*Standard deviation*, déviation standard
SFR	Société Française de Rhumatologie
SoC	*Standard of care drugs*, traitements prophylactiques conventionnels
SU level	*Serum urate level,* taux sanguin d'urate
T2T	*Treat-to-target*, traitement jusqu'à la cible
tC	*Total cholesterol*, cholestérol total
TG	*Triglycerides*, triglycérides
ULT, THU	*Urate Lowering Therapy*, Traitement Hypo-Uricémiant
VTE	*Venous thromboembolism*, maladie thrombo-embolique veineuse
XOI	*Xanthine oxidase inhibitor*, inhibiteur de la xanthine oxydase
[IL1]i	*Interleukine 1 [IL1] inhibitor*, biothérapie anti-interleukine 1

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Préambule

Le travail scientifique présenté dans cette thèse de médecine fait l'objet d'une publication d'article international en anglais. Il suit le plan suivant :

- Une introduction longue en français, qui poursuit deux objectifs : présenter le contexte médical avec une orientation principalement pédagogique, et présenter le contexte scientifique et l'objectif, comme le fait également l'introduction de l'article en anglais
- L'abstract en anglais, tel qu'il sera soumis en complément de l'article reproduit juste après.
- L'article en anglais, tel qu'il sera soumis à une revue scientifique internationale. Cet article suit le plan classique, dans le format imposé par le journal (introduction, matériel et méthodes, résultats, discussion)
- Une discussion en français, qui reprend pour l'essentiel la discussion en anglais de l'article

Le document est structuré ainsi en application de la circulaire Toubon[1].

Les références présentées en fin de document, ainsi que les listes de figures et tables, résultent de la fusion des parties en anglais et en français. La numérotation est donc incrémentée dans l'ensemble du document, que les parties soient anglophones ou francophones.

[1] Circulaire du 19 mars 1996 concernant l'application de la loi no 94-665 du 4 août 1994 relative à l'emploi de la langue française. JORF n°68 du 20 mars 1996 page 4258. NOR: PRMX9601403C

Introduction générale

1 Rationnel de l'étude

La goutte est le rhumatisme inflammatoire le plus fréquent chez les hommes de plus de 40 ans. Sa prévalence actuelle est évaluée à 0,9% en France [1], et est actuellement en augmentation à la fois dans les pays industrialisés et émergents [2]. La hausse de la prévalence de la maladie semble être expliquée d'une part par le vieillissement de la population, et d'autre part par la prévalence croissante des comorbidités cardio-vasculaires [3]. Cette arthropathie, induite par des cristaux d'urate monosodique (UMS) se déposant dans les articulations et les tissus péri-articulaires, fait suite à une hyperuricémie prolongée [4]. Il s'agit de la seule arthropathie à microcristaux curable [3].

L'hyperuricémie est communément définie comme un taux sanguin d'urate constamment supérieur à son point de saturation. Son seuil est estimé à 6,8 mg/dL (416µmol/L) dans des conditions physiologiques de pH et de température [3]. Elle est d'origine multifactorielle, génétique et environnementale : des études réalisées en population ont montré des variations de l'uricémie selon le sexe, l'ethnie, le mode de vie, ce qui ne modifie pour autant pas son point de saturation.

L'hyperuricémie est considérée comme le facteur de risque principal voire unique de goutte. Cependant, malgré le lien très étroit entre hyperuricémie et goutte, une hyperuricémie isolée ne suffit pas à poser le diagnostic de goutte. En effet, seuls 10 à 15% des hyperuricémies chroniques développeront des signes cliniques de goutte, selon une relation temporelle habituellement décrite en 3 temps : l'hyperuricémie asymptomatique, les crises aiguës de goutte, et l'arthrite goutteuse chronique. De nombreuses études épidémiologiques laissent penser qu'en rapport avec le syndrome métabolique, elle serait aussi un terrain favorable au développement de l'obésité, du diabète, de la stéatose hépatique non alcoolique, de l'hypertension artérielle (HTA), et des maladies cardiovasculaires et rénales [5].

Le degré d'hyperuricémie est un facteur prédictif fort de la survenue de crises de goutte [6]. Sa limite pathologique est communément fixée à 6mg/dL (360µmol/L) car le risque de goutte semble apparaître au-delà de cette valeur, le seuil de

solubilisation des cristaux d'UMS étant abaissé au niveau des extrémités où la température est plus basse [7]. La persistance d'une hyperuricémie est étroitement liée à la récidive des crises aigües et à l'apparition de complications de la goutte [3]. A noter que cette uricémie ne doit pas être inférieure à 40 mg/L, car en deçà de ce seuil l'acide urique est cérébro-protecteur et anti oxydant (REFERANCE).

Cliniquement, une crise aiguë de goutte se manifeste par un épanchement articulaire inflammatoire douloureux de survenue brutale, classiquement de localisation podagre, souvent associé à une impotence fonctionnelle majeure, et régressant spontanément en 5 à 10 jours [8]. Elle correspond à la précipitation d'urate dans l'articulation [9].

Le ***diagnostic*** de goutte est porté sur la mise en évidence des cristaux d'UMS par l'intermédiaire d'une ponction articulaire (gold standard), ou par la réalisation d'une imagerie complémentaire lorsqu'il n'est pas possible de réaliser une ponction articulaire [9]. L'échographie articulaire permet de détecter précocement des signes de maladie goutteuse (successivement agrégats, puis signe du double contour, puis tophus) [10]. Selon des publications récentes issues des données de la cohorte USEFUL, elle pourrait aussi avoir un intérêt pour le suivi [11,12]. Les radiographies standards n'ont d'intérêt que dans les stades avancés de goutte lorsque les lésions d'arthropathie sont installées (érosions en hallebarde) [13]. Le scanner double-énergie (DECT) peut confirmer la présence de microcristaux de goutte, mais celui-ci est encore rarement utilisé en pratique clinique quotidienne [14]. L'uricémie peut être normal ou abaissée lors d'une crise, et peut être augmentée au cours d'autres pathologies, comme lors d'une arthrite septique. Le dosage du taux sanguin d'urate, hors crise, est recommandé pour le diagnostic ainsi que pour la « titration » des posologies de traitement hypouricémiant (THU) lors du suivi [9].

Les critères de classification développés par l'*American College of Rheumatology / European League Against Rheumatism (ACR / EULAR)* en 2015 (**Figure 1**), destiné aux inclusions de patients dans les protocoles de recherche, peuvent aussi aider au diagnostic de goutte en soins primaires, notamment si la ponction articulaire est impossible, avec une sensibilité de 92% et une spécificité de 89% [15].

Criteria		Categories	Score
CLINICAL	Pattern of joint/bursa involvement	Ankle OR midfoot (mono-/oligo-)	1
		MTP1 (mono-/oligo-)	2
	Characteristics of episode(s) ever	One characteristic	1
		Two characteristics	2
		Three characteristics	3
	Time-course of episode(s) ever	One typical episode	1
		Recurrent typical episodes	2
	Clinical evidence of tophus	Present	4
LAB	Serum Urate	<4mg/dL [<0.24mM]	-4
		6-<8mg/dL [0.36-<0.48mM]	2
		8-<10mg/dL [0.48-<0.60mM]	3
		≥10mg/dL [≥0.60mM]	4
	Synovial Fluid examination for MSU crystals	negative	-2
IMAGE	Imaging evidence of urate deposition	Present	4
	Imaging evidence of gout-related joint damage	Present	4
		Maximum Possible Total Score	**23**

Figure 1. Critères ACR/EULAR 2015 : diagnostic de goutte retenu si score ≥ 8

Concernant les ***complications*** de la goutte, elles sont liées à l'accumulation tissulaire de cristaux d'UMS au fil des années [16,17]. Elles dépendent des facteurs étiologiques, de la durée d'évolution, et du délai de prise en charge de la goutte. Elles sont l'apparition de tophus sous cutanés, les crises de colique néphrétique, l'insuffisance rénale, et l'arthropathie uratique.

Les ***profils des patients goutteux*** sont multiples, liés aux causes d'hyperuricémie et de goutte, et touchent des populations jeunes comme plus âgées. Il peut s'agir d'un défaut d'élimination d'acide urique, d'origine génétique (polymorphismes des transporteurs de l'urate au niveau rénal, hépatique ou entérocytaire) [18], ou médicamenteux (dont les diurétiques) [19]. Il peut aussi s'agir d'un excès de production, d'origine génétique (enzymopathies), ou sur une augmentation du turn-over cellulaire (notamment dans les syndromes myéloprolifératifs ou lymphoprolifératifs, les traitements cytolytiques ou le psoriasis), ou sur un excès d'apport alimentaire (bières, sodas sucrés [20], viandes et produits de

la mer [21]). La présence de comorbidités rénales, métaboliques et cardiovasculaires est fréquente chez les patients goutteux, compromettent leur pronostic, et sont sources de difficultés thérapeutiques [22,23].

Concernant son ***poids économique***, selon un recueil sur base de données hospitalières entre 2009 et 2011, la goutte représentait 60% des hospitalisations pour arthropathie microcristallines, soit un coût de soins évalué à 37 millions d'euros [4]. L'âge moyen des patients goutteux hospitalisés était de 69,7 ± 14,7 ans, et 70% étaient des hommes. Ils présentaient une fréquence plus élevée de comorbidités cardiovasculaires (HTA, diabète, dyslipidémie, cardiopathies ischémiques) et rénales (insuffisance rénale chronique). Les facteurs retrouvés comme explicatifs de la récurrence des hospitalisations étaient une posologie insuffisante d'Allopurinol (ALLO) et la faible observance du THU, en plus des complications liées aux comorbidités. Ainsi, le respect des recommandations de prise en charge de la goutte pourrait permettre de limiter ce fardeau économique.

La ***prise en charge médicamenteuse*** est la plus efficace dans la goutte. Les traitements de fond sont des traitements hypouricémiants, dont les plus prescrits sont l'ALLO et le Febuxostat (FBX), des inhibiteurs de la xanthine oxydase (XOI). Ils sont simples et peu coûteux. Leurs objectifs thérapeutiques incluent le contrôle des crises aiguës et la prévention de leur récurrence, ainsi que la prévention ou la réversibilité des complications chroniques de la goutte [25]. Le principe est très simple : en abaissant l'uricémie à un niveau inférieur à son point de saturation, cela empêche la formation de cristaux et dissout les cristaux existants [25], sans lesquels il n'y a plus de crise de goutte. Sur le plan rhumatologique, lorsque ces traitements sont correctement prescrits et pris, ils permettent de guérir la quasi-totalité des patients dans les essais cliniques. Sur le plan extra-rhumatologique, on connaît assez bien leur profil de tolérance [27], mais assez peu leurs effets bénéfiques extra-rhumatologique, cardiaques et rénaux notamment.

En parallèle, il est tout de même conseillé de prendre en charge les facteurs de risque d'hyperuricémie, comme le surpoids ou le régime alimentaire riche en purines ou fructose, qui permettent toutefois rarement à eux seuls de modifier l'uricémie et l'évolution de la maladie [27].

Concernant ***l'objectif d'uricémie*** à atteindre sous traitement, il est sans doute discutable selon le point de vue du médecin et le profil du patient. Selon les dernières recommandations, l'objectif est d'obtenir sous traitement une uricémie au moins inférieure à 360μmol/L (6 mg/dL), voire inférieure à 300μmol/L (5 mg/dL) [7,29]. Des auteurs ont montré que plus l'uricémie est basse plus la diminution de la taille des tophi est rapide, mais nous ne disposons actuellement pas d'essai thérapeutique confirmant une cible à 5mg/dL en cas de goutte tophacée [29]. Ces limites sont discutée par d'autres équipes qui affirment que la cible d'uricémie doit être individualisée, notamment vers des objectifs d'uricémie plus bas [31]. On rappelle cependant qu'il est recommandé de maintenir une uricémie supérieure à 4.0 mg/dL, car il existerait des conséquences néfastes au maintien d'une uricémie trop basse.

Malgré une bonne compréhension de la maladie et des traitements simples et peu coûteux, les données observationnelles de « vraie vie » de la prise en charge des patients montrent que la majorité des patients ne sont pas à l'objectif thérapeutique et font encore des crises de goutte à répétition [32-34].

Concernant les ***obstacles aux soins***, on peut noter les fausses idées sur la maladie parfois partagées par les médecins, comme le manque de conscience sur la sévérité potentielle de la maladie [2], des prises en charge thérapeutiques non concordantes avec les recommandations proposées par les sociétés savantes (prescription d'ALLO à posologie sous maximale) [9], antérieurement le manque d'une valeur commune reconnue d'uricémie cible rendant plus difficile l'adhésion des patients au traitement [7], une mauvaise compréhension des objectifs du traitement et sa lenteur d'action induisant une mauvaise observance du patient [25]. Il a pourtant été montré à de nombreuses reprises dans la littérature une augmentation de la mortalité en cas de non prise en charge de la goutte, avec notamment un risque relatif de mortalité globale à 1,08 et de mortalité cardiovasculaire à 1,20 [35].

Diverses recommandations des sociétés savantes de rhumatologie ont été émises au cours de ces dernières années : par l'*EULAR* en 2006 et 2016 [36], par l'*American College of Physicians (ACP)* en 2016 [37,38], par la *British Society of Rheumatology (BSR)* en 2017 [39], et par l'*ACR* en 2012 [40,41]. Les divergences

entre ces différentes recommandations résultent d'un manque de données scientifiques solides.

Aux Etats-Unis, les nouveaux cas de goutte coûtent 27,4 millions de dollars par an [42]. En 2012, une enquête nationale américaine a été réalisée auprès d'un échantillon aléatoire de médecins de soins primaires, pour évaluer leur prise en charge de la goutte aiguë, intercritique et tophacée, en la comparant aux recommandations européennes et américaines publiées par les sociétés savantes [43]. Cette enquête, réalisée auprès d'environ 850 médecins dont la moitié avaient plus de 16 ans d'expérience, notait principalement une sous-prescription et une posologie inappropriée de THU, et l'absence de traitement prophylactique prescrit en parallèle de l'introduction du THU. Au total, seul 50% des médecins en soins primaires pratiquent un traitement optimal pour la gestion de la goutte aiguë, et moins de 20% pour la goutte intercritique ou tophacée, et l'éducation thérapeutique des patients (ETP) était peu pratiquée.

Les médecins généralistes américains remettent actuellement en cause l'intérêt de la prise en charge proposée par les autres sociétés savantes. La publication de l'*ACP* de novembre 2016 se base uniquement sur des données d'essais contrôlés randomisés [37,38], et va jusqu'à remettre en cause la nécessité de réduire le taux d'acide urique pour guérir de la goutte. Ils arguent une paucité d'essais randomisés pour confirmer la pertinence des autres recommandations.

La pertinence d'abaisser le seuil d'uricémie a été démontrée formellement depuis, par une étude anglaise conduite avec des infirmières suivant strictement les recommandations de prise en charge versus la prise en charge habituelle faite en médecine générale [26].

Dans ce contexte, ***des recommandations sur la prise en charge de la goutte ont été publiées en 2020***, pour la première fois en France par la SFR [29,44], alors que parallèlement l'*ACR* mettait à jour ses recommandations américaines [45]. Elles sont issues des données de nombreuses études observationnelles et d'avis d'experts, et ont pour objectif de donner des informations uniformes et claires, pour faciliter leur application dans la pratique quotidienne et l'ETP. Ces deux recommandations

confirment l'intérêt du *treat-to-target* (T2T) dans la goutte, stratégie déjà suggérée un peu avant leur publication [46].

Cependant, pour les appuyer, nous ne disposons pas de données dans la littérature concernant les résultats de la prise en charge en centres experts, où les recommandations sont potentiellement les plus respectées, les rhumatologues de ces centres experts étant à l'origine des recommandations de nationales et internationales.

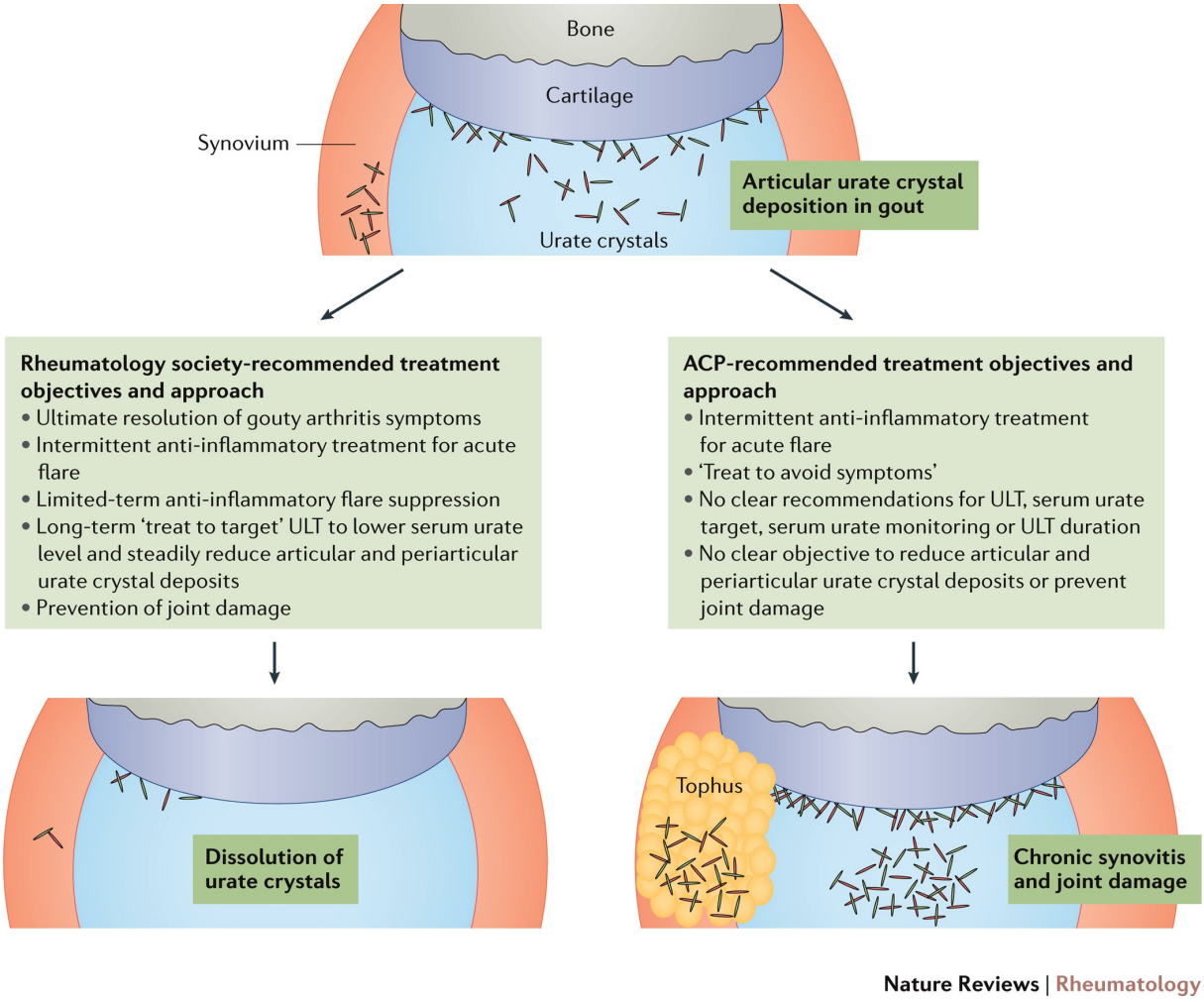


Figure 2. Comparaison schématique des résultats clinico-pathologiques attendus de la goutte à partir des recommandations pour la prise en charge de la goutte [38].

2 Recommandations françaises de 2020 de prise en charge de la goutte par la SFR

En 2020, la SFR a publié ses premières recommandations sur la prise en charge de la goutte [29,44]. Ce travail, basé sur les recommandations de l'*EULAR* de 2016, est le résultat d'une revue de la littérature réalisée entre janvier 2016 et avril 2019 via PubMed, sur tous les aspects de prise en charge de la goutte chronique. Les données récupérées ont ensuite été analysées par un groupe de travail afin d'établir des recommandations simples et facilement compréhensibles sans objectif d'exhaustivité. Elles ont ensuite été relues et validées par la SFR, puis par un groupe de médecins libéraux rhumatologues et généralistes.

2.1 Principes fondamentaux et recommandations spécifiques concernant les traitements de fond hypouricémiants [29]

Trois principes fondamentaux ont été établis dans ces recommandations, que sont la nécessité d'une ETP pour le succès à long terme de la prise en charge recommandée, la compréhension par le patient de la nécessité d'abaisser le taux sanguin d'urate par un THU, et la nécessité pour le médecin d'informer le patient sur les complications de cette pathologie et les nécessités d'adaptation du mode de vie.

Cinq recommandations spécifiques ont été établis.

L'introduction d'un THU dès le diagnostic de goutte établi apparaît pour la première fois dans des recommandations.

Un objectif d'uricémie minimalement inférieur à 360µmol/l (6 mg/dl) est recommandé chez tous les patients goutteux, mais si possible inférieur à 300µmol/l (5 mg/dl).

Le choix de THU est adapté à la fonction rénale. Lorsque le débit de filtration glomérulaire estimé (DFGe) est supérieur à 60 ml/min/1,73 m2, l'ULT de première intention est l'ALLO (dose initiale de 50 à 100 mg par jour, à augmenter par paliers de 50 à 100 mg par jour toutes les 2 à 4 semaines jusqu'à ce que la cible d'urate sérique soit atteinte), lorsque le DFGe est compris entre 30 et 60 ml/min/1,73 m2, l'utilisation de l'ALLO doit être prudente et le FBX peut être considéré comme une

alternative, lorsque le DFGe est inférieur à 30 ml/min/1,73 m2, l'ALLO doit être évité et le fébuxostat doit être préféré. L'utilisation du fébuxostat doit être prudente chez les patients souffrant de maladies cardiovasculaires graves.

La prescription d'un traitement prophylactique des crises, conjointe au THU, est indiquée pour une durée minimum de 6 mois en l'absence de contre-indication.

La recherche et la prise en charge des comorbidités de la goutte doit être réalisée.

Des limites ont été évoquées dans ces recommandations.

Dans un objectif de concision, et non d'exhaustivité, seuls les THU classiquement utilisés sont mentionnés. Le moment idéal auquel ils doivent être introduits n'est pas précisé, puisque des études de faible envergure commencent à sous-tendre une introduction possible per critique sous couvert d'un traitement anti inflammatoire bien mené, contrairement à la pratique actuelle française préférant une introduction à distance pour éviter l'aggravation de la crise en cours [47].

Ces recommandations se basent sur des études pour la plupart observationnelles et en soins primaires, et la recommandation d'introduction d'un THU chez tout patient ayant présenté une première crise de goutte est basée sur un avis d'expert. Ainsi, la stratégie de viser un objectif précis d'uricémie, prônée par l'ensemble des sociétés savantes de rhumatologie, appelle à la réalisation d'essais randomisés sur cette thématique.

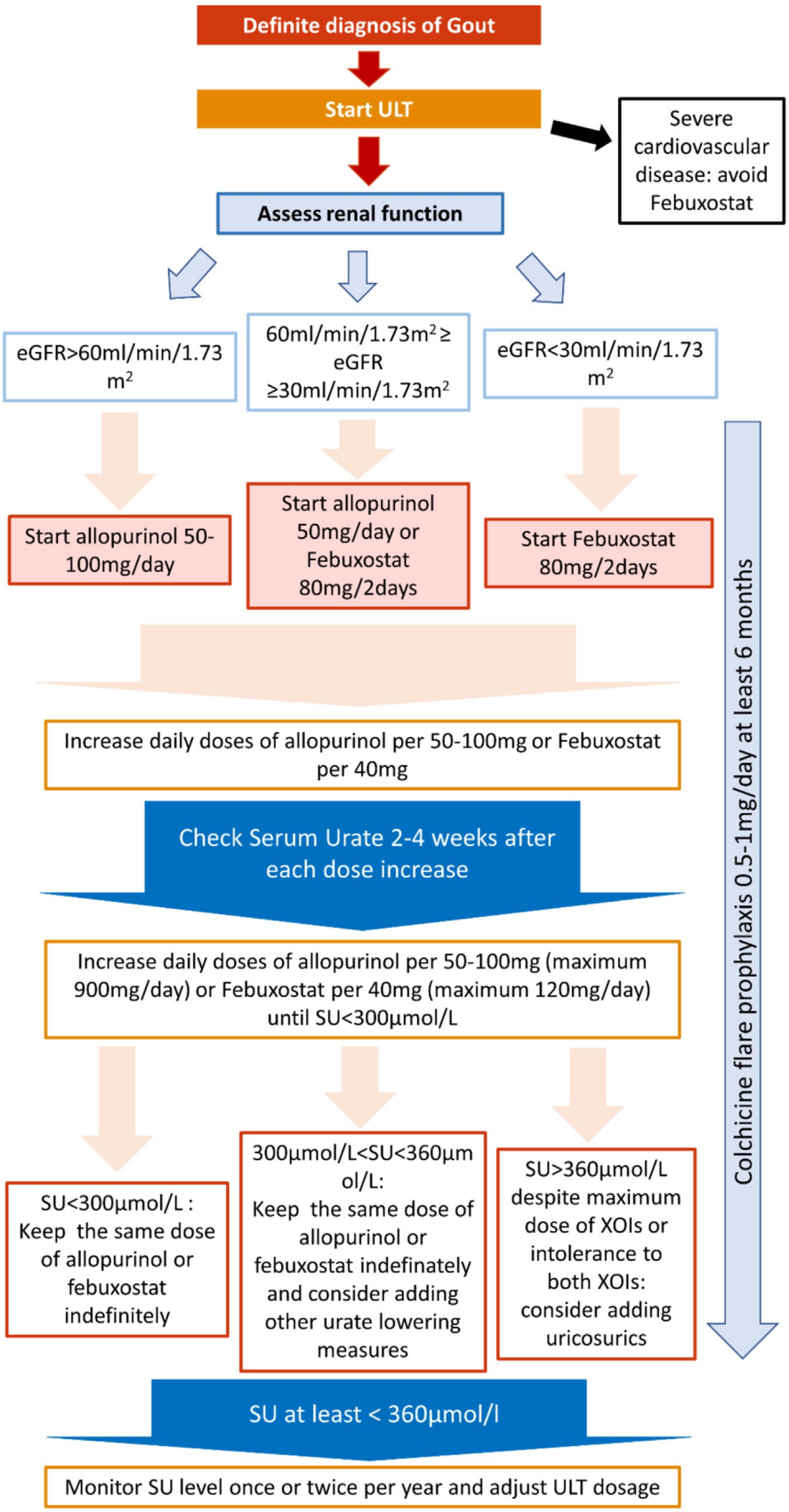


Figure 3. Gestion de la prescription d'un traitement hypouricémiant selon les recommandations de la Société Française de rhumatologie (2020) [28]

2.2 Principes fondamentaux et recommandations spécifiques des traitements de crise aiguë de goutte [44]

4 principes généraux ont été établis.

Le patient doit être informé de l'importance de traiter la crise de goutte dès ses premiers signes ; il doit pouvoir s'auto-médiquer selon un traitement pré-défini, expliqué et prescrit par son médecin.

Le patient doit savoir que le traitement de la crise ne suffit pas à traiter la goutte, et doit connaître l'importance du THU, qui seul peut soulager définitivement les symptômes de la goutte.

Le choix du traitement de la crise de goutte dépend des comorbidités (maladies cardiovasculaires, insuffisance rénale, diabète, ulcère gastro-duodénal, infections), des antécédents d'intolérances médicamenteuses, des interactions médicamenteuses potentielles, du nombre et du type d'articulations touchées.

Les médicaments qui peuvent être utilisés pour le traitement de la crise sont : la Colchicine, les anti-inflammatoires non-stéroïdiens (AINS) per os, la corticothérapie orale ou intra-articulaire, et les inhibiteurs de l'IL-1 ([IL1]i). D'autres moyens peuvent être associés : repos et glaçage articulaires, médicaments antalgiques.

4 recommandations spécifiques ont été établies.

La colchicine doit être initiée le plus tôt possible, idéalement dans les 12 premières heures, à la posologie suivante : 1 mg dès le début de la crise, suivi de 0,5 mg une heure plus tard, et poursuivie les jours suivants à 0,5 mg × 2–3/jour en fonction de l'évolution. La diarrhée est le premier signe de toxicité et doit faire diminuer ou arrêter le traitement. La posologie de la colchicine doit être diminuée chez l'insuffisant rénal et en cas de co-prescription de médicaments qui interfèrent avec son métabolisme.

La corticothérapie orale doit être prescrite à la dose de 30 à 35 mg/j (équivalent prednisolone) pendant 3–5 jours. Elle est déconseillée en cas de diabète de type 2 ou d'hypertension artérielle déséquilibrés. La corticothérapie intra-articulaire doit être privilégiée pour le traitement d'une arthrite facilement accessible à un geste local.

Les AINS doivent être prescrits per os et sur une courte période, le temps de la crise. Ils doivent être évités en cas d'insuffisance rénale stade 3–5 ou de maladie cardio-vasculaire sévère.

Les [IL1]i doivent être initiés en milieu hospitalier, et réservés aux cas d'échec ou de contre-indication aux AINS, aux corticostéroïdes et à la colchicine. Ils sont contre-indiqués en cas d'infection et doivent faire surveiller les polynucléaires neutrophiles. Augmentant le risque d'infection sévère, et devant leur coût bien plus élevé que celui des autres traitements de crise de goutte, ils ne peuvent être considérés qu'en deuxième intention.

À l'instar des recommandations EULAR de 2016, le groupe de travail conseille également de considérer l'association de médicaments anti-inflammatoires (par exemple, colchicine et corticostéroïdes) dans le traitement des crises de goutte.

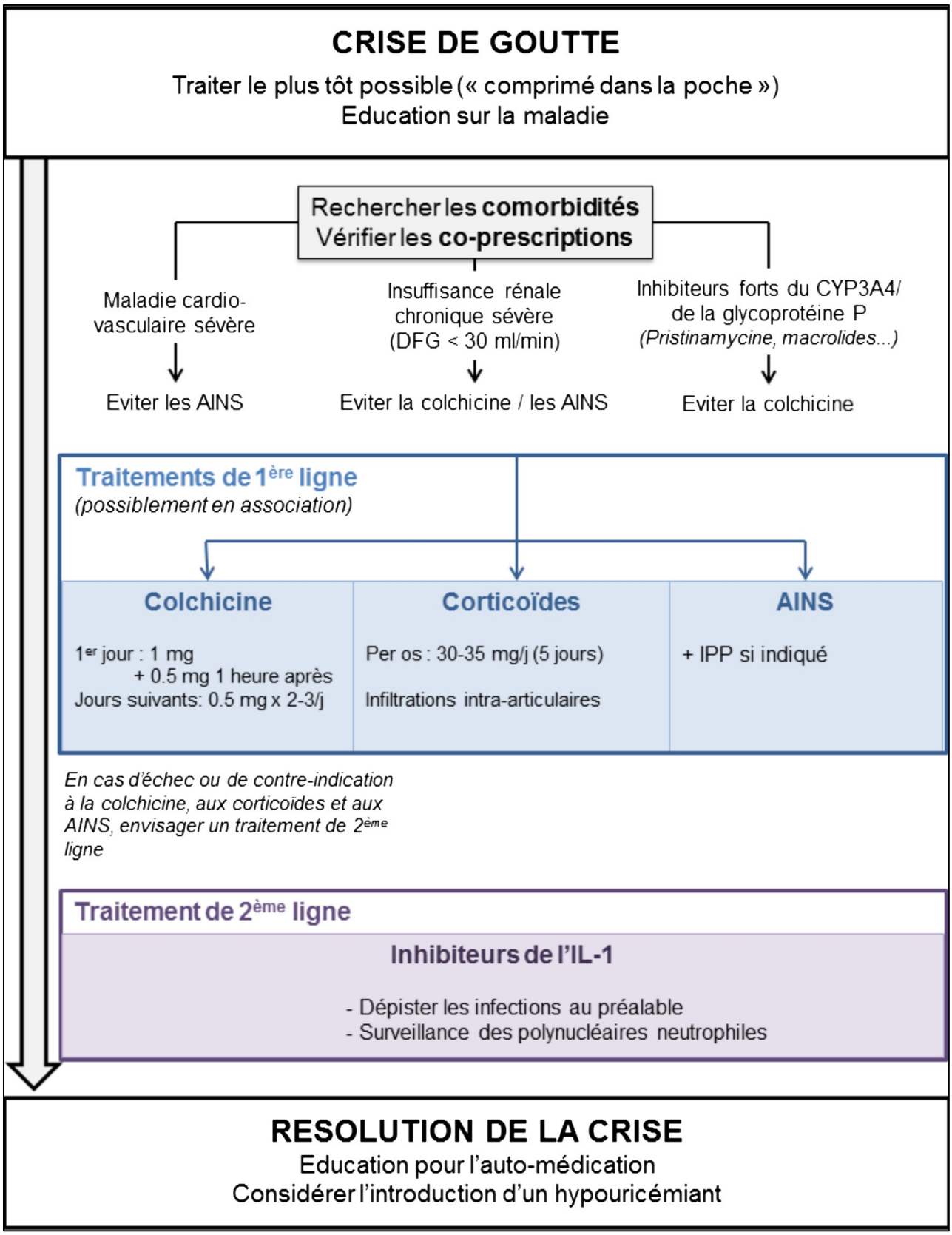


Figure 4. Stratégie de prise en charge des crises de goutte. *DFG: débit de filtration glomérulaire estimé ; IL-1 : interleukine 1 ; AINS : anti-inflammatoires non stéroïdiens ; IPP : inhibiteur de la pompe à proton.*

2.3 Comparaison des recommandations 2020 de la SFR avec les recommandations 2020 de l'ACR

Les recommandations de l'*ACR* 2020 concernant la prise en charge de la goutte font état de 42 recommandations, contre les 16 principes généraux et recommandations spécifiques proposés par les recommandations françaises. La démarche de méta-analyse entre ces 2 groupes d'étude était relativement similaire.

Concernant le THU, son indication reste conservatrice par rapport aux recommandations internationales et est retenue pour tous les patients présentant des poussées de goutte à répétition, des lésions radiographiques dues à la goutte, ou atteints de goutte tophacée. Le choix dans les recommandations françaises d'élargir l'indication de THU à tous les patients goutteux a pour objectif de simplifier la décision d'introduction des traitements afin de lutter contre leur sous-utilisation. On note une indication d'ALLO comme THU de première intention plus large, y compris en cas d'insuffisance rénale chronique modérée à sévère (CKD ; stade > 3), là où le choix entre ALLO et FBX est laissé dans les recommandations françaises. Des recommandations sont proposées pour les THU autres que les XOI. La cible d'uricémie est définie inférieure à 360µmol/l (6 mg/dl) pour tous les patients, soit un objectif plutôt moins strict que dans les recommandations françaises.

Concernant le traitement prophylactique, il est recommandé seulement 3 à 6 mois, avec une recommandation au même niveau de la colchicine, des AINS, et des corticoïdes, contrairement à la SFR qui recommande la colchicine en première intention. L'*ACR* et la SFR se positionnent au même niveau sur les indications du traitement par [IL1]i.

3 Place des traitements de crise et hypouricémiants non mentionnés dans les recommandations de la SFR 2020

3.1 Traitements de fond

Les THU classiquement utilisés dans la goutte, car ayant leur place en première intention dans les recommandations internationales, sont les XOI (ALLO et FBX). Il existe d'autres classes thérapeutiques moins utilisées, non mentionnées dans les recommandations de la SFR 2020 mais mentionnées dans les recommandations de l'*ACR* et de l'*EULAR* [36,45].

Les uricosuriques (Probénécide et Benzobromarone) sont disponibles en France et peuvent être prescrit en bithérapie avec un XOI. Ils sont rarement utilisés du fait d'un profil de tolérance encore insuffisamment connu, notamment concernant les interactions pharmacologiques du Probénécide, et l'hépatotoxicité de la Benzbromarone [27]. La Benzobromarone serait plus efficace que le Probénécide sur l'abaissement de l'uricémie, mais après un retrait du marché en 2003 pour de rares cas d'hépatotoxicité grave, il est depuis 2005 disponible seulement en autorisation temporaire d'utilisation (ATU) en cas d'échec de l'ALLO et du Probénécide [9].

Les uricases (agents uricolytiques), sont soit indisponible (Pégloticase), soit non approuvées (Rasburicase) en France.

Enfin, le Lesinurad (inhibiteur sélectif de transporteurs rénaux de l'acide urique), utilisé en association avec un XOI, est reconnu par la SFR comme une stratégie efficace d'atteinte de la cible dans les gouttes réfractaires à un XOI seul [29,48]. Malgré son AMM, il est toujours en attente de remboursement en France où il est probable qu'il ne l'obtienne pas.

La SFR juge actuellement que les patients réfractaires aux XOI seraient probablement rares, si la titration de posologie du médicament XOI était correctement réalisée [29]. En effet cela est corroboré par des études françaises montrant l'absence de modification significative de la posologie quotidienne d'ALLO, et l'absence de modification du pourcentage de patient atteignant la cible entre 2008 et 2014, malgré une biologie en faveur d'une modification [49,50].

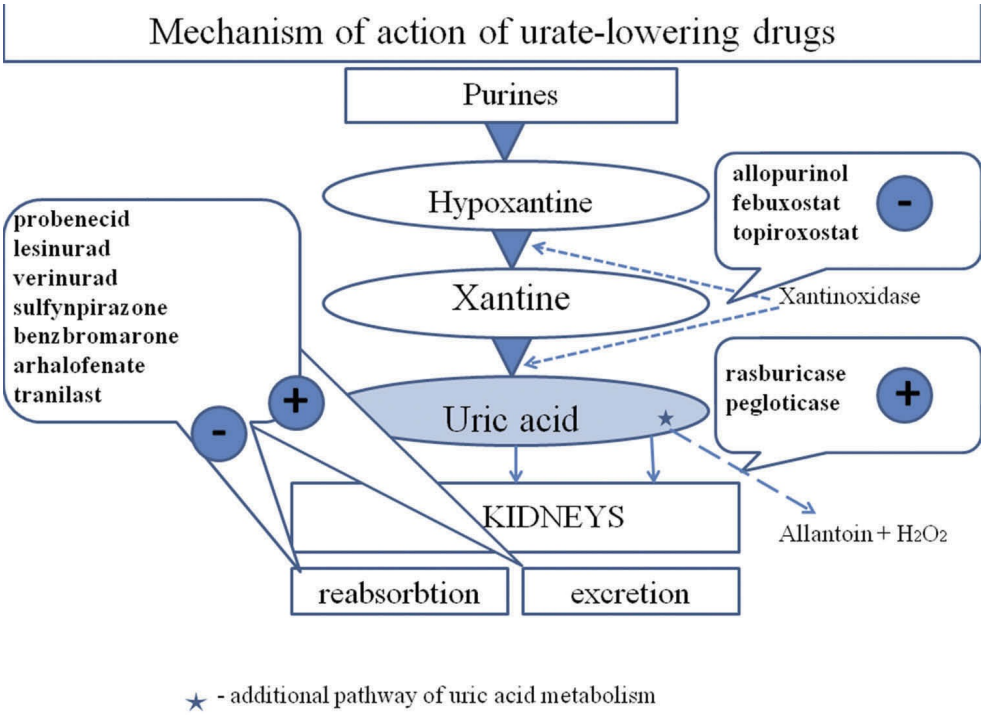


Figure 5. Mécanisme d'action des traitements hypouricémiants. [27]

3.2 Traitements de crise

Les prescriptions de traitements prophylactiques conventionnels (*SoC*) que sont la Colchicine, la corticothérapie et les AINS, sont abordées dans les recommandations 2020 de la SFR.

Concernant les [IL1]i, les indications théoriques sont reprécisées dans les recommandations de la SFR, mais leur prescription initiale hospitalière (PIH) se confronte aux strictes recommandations récemment émises par l'EULAR et l'*European Medicines Agency* (EMA).

Le rationnel d'utilisation des [IL1]i par rapport aux thérapies conventionnelles, est lié à la difficulté de prise en charge des poussées polyarticulaires et/ou chez des patients poly-pathologiques, s'incluant dans le concept de '*difficult-to-treat*' (*DTT*) gout [51]. Dans ces conditions, les traitements prophylactiques conventionnels (*SoC*) sont insuffisant, du fait des nombreuses contre-indications et interactions médicamenteuses qu'ils présentent [9].

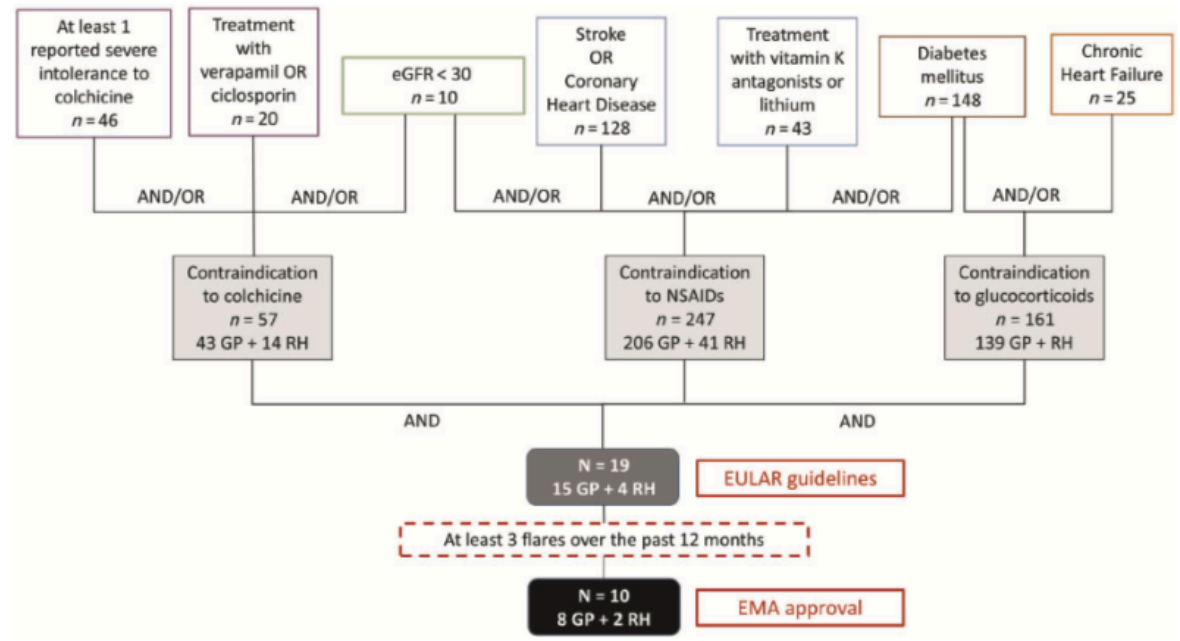
Deux [IL1]i sont principalement utilisées aujourd'hui :

- le **canakinumab** (ILARIS®, anticorps monoclonal humain ciblant spécifiquement l'interleukine-1β) : il a l'avantage de ne s'administrer qu'en une seule injection mensuelle, mais son coût est élevé (11 361,17 € l'injection),
- l'**anakinra** (KINERET®, antagoniste recombinant du récepteur de l'IL1, c'est-à-dire anti-IL1α et anti-IL1β) : il nécessite une injection quotidienne sur une durée maximale de 5 jours, mais présente un intérêt économique (220,77€ l'injection).

Les indications des [IL1]i, retenues par l'*EULAR* et par l'*EMA* dans la prise en charge des crises aigües, présentent quelques divergences [52]. Pour l'*EMA*, ce traitement est indiqué chez des patients adultes ayant des crises fréquentes (au moins 3 crises au cours des 12 mois précédents), chez qui les AINS et la Colchicine sont contre-indiqués, mal tolérés ou n'entrainent pas de réponse suffisante et chez qui des cures répétées de corticoïdes ne sont pas appropriées. Pour l'*EULAR*, l'indication est similaire en dehors du fait que le seuil minimum de 3 crises par an n'est pas imposé. Selon Pascart et al., les difficultés rencontrées avec ces recommandations étaient liées à une éligibilité très restreinte aux [IL1]i, les critères de l'*EMA* excluant la moitié des patients éligibles selon les critères de l'*EULAR* [52].

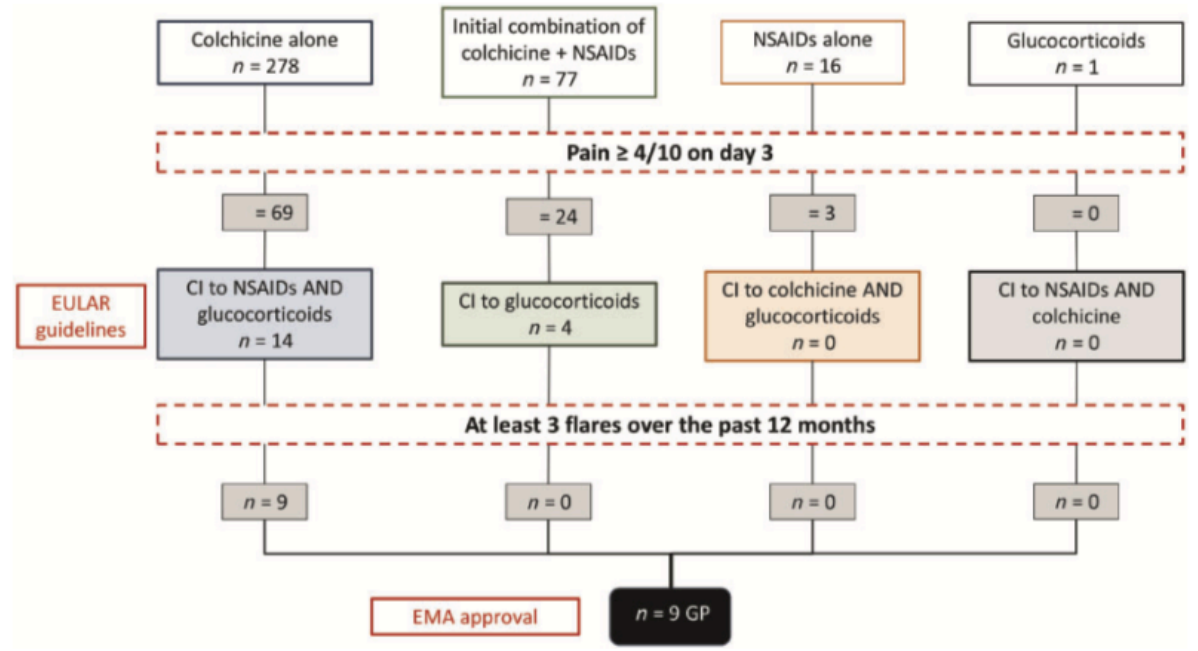
A visée comparatives, les recommandations de l'*ACR* et la SFR sont moins strictes et retiennent l'indication des [IL1]i dès lors que les autres traitements anti-inflammatoires sont inefficaces, mal tolérés ou contre-indiqués [44,45]. Selon l'*ACR*, la prescription d'[IL1]i est à préférer plutôt que l'absence de traitement de crise [45].

En France, bien que l'Anakinra soit la molécule habituellement prescrite notamment pour son intérêt économique [53], seul le Canakinumab a une AMM dans la prise en charge symptomatique des crises aiguës de goutte depuis 2013, suivant les indications retenues par l'EMA. Le profil de tolérance de ces 2 thérapeutiques [IL1]i est comparables.



Eligibility to first-line IL-1β inhibition therapy ($n = 1003$) according to the combination of contraindications and/or intolerance to colchicine, NSAIDs and glucocorticoids, and the number of flares in the past 12 months. EMA approval refers to canakinumab SPC. Follow-up of patients by GPs or RHs. eGFR according to Cockroft and Gault formula. eGFR: estimated glomerular filtration rate; EMA: European Medicines Agency; GP: general practitioner; RH: private practice rheumatologist; SPC: summary of product characteristics.

Figure 6. Eligibilité à un [IL1]i en première ligne selon l'EULAR et l'EMA [52].



Eligibility for second-line canakinumab therapy during flares treated from baseline ($n = 487$) because of insufficient treatment response after first-line SoC treatment and contraindications to the remaining available SoC treatments. EMA approval refers to canakinumab SPC. CI: contraindication; EMA: European Medicines Agency; GP: general practitioner; SoC: standard of care; SPC: summary of product characteristics.

Figure 7. Eligibilité au Canakinumab en deuxième ligne pour la prise en charge d'un épisode aigu de goutte [52].

4 Justification de l'intérêt publique de notre étude

L'intérêt de cette étude est de démontrer que, lorsque la prise en charge de la goutte est réalisée en respectant les pratiques recommandées, elle permet d'obtenir une majorité de patient à la cible thérapeutique, contrairement aux données publiées dans la littérature sur la prise en charge actuellement réalisée en routine respectant peu les recommandations. Ceci renforcerait la nécessité de mettre en application, notamment en soins primaires, les recommandations françaises, volontairement simples, sur la prise en charge de la goutte.

La description des profils des patients goutteux pris en charge en centre expert sera informative pour communiquer sur le type de patients nécessitant une prise en charge dans ces centres, et appuyer à terme la constitution formelle de centres de référence.

5 Objectif

L'objectif principal est d'évaluer les résultats de prise en charge des patients goutteux suivis dans des centres experts français, participants à l'élaboration des recommandations françaises pour la prise en charge de la goutte, sur le contrôle de l'uricémie et la prévention des crises de goutte.

Les objectifs secondaires sont les suivants :

a. Déterminer le profil des patients suivis dans ces centres experts.

b. Déterminer les facteurs associés à l'atteinte de l'objectif thérapeutique (maîtrise de l'uricémie au cours du suivi).

c. Déterminer la concordance de la prise en charge en centre expert de la goutte avec les recommandations.

d. Décrire l'utilisation des [IL1]i

e. Décrire l'objectif de l'utilisation de l'imagerie au diagnostic

f. Décrire les effets secondaires des traitements de crise et de fond de la goutte

Dans un premier article, nous expliciterons le profil des patients goutteux et leur prise en charge en centre tertiaire.

Dans un second article, nous mettrons en rapport les résultats de prise en charge sur le plan rhumatologique et extra-rhumatologique, et les facteurs associés à un bon ou mouvais résultat de prise en charge.

Premier article en Anglais
URATE CHALLENGE 1

Gout patients profile and management in referral centres: results of a real-world multicentric study

1 Abstract

Objective: Gout is very poorly managed in primary care. We have no data on its management and outcomes in referral centres. The primary objective was to evaluate the outcomes of gout patients' management in French referral centres, on the control of serum urate level (SU level) (<360µmol/L), and on the prevention of gout flares. The secondary objectives were to determine patients' profiles, management consistency with the recommendations, and to describe the use of advanced imaging.

Methods: Our study population was a cohort of 300 gout patients, randomly included from the consultation lists of rheumatologists in 3 French expert centres, and evaluated at inclusion (M0, between 2016 and 2019), then at 6 months (M6), 1 year (M12) and 2 years (M24). We performed descriptive analyses on patients' profile and management, and bivariate analyses to compare the different sub-populations.

Results: Consistency with the 2020 French recommendations was respected for 95% of the patients. Among those not lost to follow-up (n= 122 at M24), targeted SU level was reached for 59.4% at M6, 67.9% at M12, and 78.6% at M24, and compliance to urate-lowering therapy (ULT) was about 85%. At M24, still 13.1% experienced flares and 9.1% suffer from chronic arthritis without flares. The background treatment was Allopurinol in 49% (mean dosage at M24 = 299.1 ± 97 mg/d), Febuxostat in 49% (mean dosage at M24 = 84.4 ± 33.3 mg/d), a uricosuric in 2% of cases. Concerning IL1 inhibitors ([IL1]i), 36 patients were eligible according to the EULAR guidelines, 15 patients according to the EMA guidelines, and finally 46 received [IL1]i at M0. 180 of the 300 patients included had an advanced imaging test during the inclusion period.

Conclusion: For most of the patients, the expert centres usually only apply a simple and optimized conventional management respecting French national guidelines, perfectly applicable in a non-specialized setting.

2 Introduction

Gout is the most common inflammatory arthritis in men over 40 years old [9]. There are actually numerous lacks in gout management in primary care and rheumatology settings, regarding both physician management and patient compliance, underpinned by an underestimation of the disease severity [54].

Several studies concerning gout patients' profile and management in primary care have already been conducted.

The French ***GOSPEL cohort*** has proposed an interesting prospective survey of about approximately one thousand gout patients in primary care and rheumatology settings [2] [49] [55], [56]. In this cohort, patients' profile and compliance of management regarding the 2006 EULAR recommendations were analysed. After 3–6 months of ULT, only around 28.5% had a SU level below 6 mg/dL (360 µmol/L), often because of too low dosage. Prophylactic treatment against flares at ULT initiation was prescribed 74.3% overall, but the dosages were often above the recommended values. Therapeutic education about lifestyle was practised in a maximum of 45% of patients. The discrepancies between real-life management of gout and current recommendation advocated for simplified recommendations, adapted to primary care management, where the vast majority of gout patients are followed-up.

In 2015 in France and Greece, the ***CACTUS cohort*** has proposed another observational analysis on about approximately three thousand gout patients, with an office-based recruitment too [57]. A large number of included patients had a history of poor compliance with their ULT, and it was concluded to a real need of PTE (patient therapeutic education).

In 2018, ***Doherty and al.*** has published a randomised controlled trial on UK data in primary care, focusing on gout management and on the effectiveness of dual follow-up by a physician and a nurse [26]. According to this study, only 40% of gout patients had a ULT, introduced by the physician without titration, and with a very poor compliance. Compliance reached almost 100% when patient education was specifically discussed, and remained high over the years [26,58].

Apart from the conventional therapeutic management of gout, other aspects are

currently discussed. ***Regarding [IL1]i prescription*** in DTT gout, two issues are currently exposed. In one hand, the EMA and EULAR recommendations are considered too restrictive and the SFR recommendations remain unclear on this subject. In the other hand only canakinumab has a marketing authorization (MA) in France whereas Anakinra is the most often prescribed in practice, for economic reasons among others. ***Regarding advanced imaging indications*** (i.e. ultrasound and DECT), they hold a high weight in the 2015 ACR/EULAR gout classification criteria, but are still underused in routine practice and their role in the management of the disease remains undefined [59]. Some studies show their probable interest in the follow-up [9,11,12].

In 2020, the SFR and the ACR published new recommendations for gout management, introducing the T2T strategy [29,45]. The French ones have been designed to give clear actualized recommendations and to be easily understood in daily practice. The fundamental principles outlined are almost all based on PTE. As indicated in their limitations, these recommendations are largely based on literature reviews of observational studies and on expert' opinions. However, currently the literature doesn't provide studies on patients' profile, on management and its outcomes, in those expert referral centres that providing recommendations. Therefore, the aim of our study was to describe the patients' characteristics, management consistency with national guidelines, and to compare outcomes of this management to the previous ones reported in usual care.

The main objective was to evaluate the proportion of patients with uricemia below 360µmol/l (6mg/dL), and the number of gout attacks, 6 months (M6), 1 year (M12) and 2 years (M24) after the beginning of referral centres' follow up. The second objectives were to evaluate baseline patients' characteristics in those expert centres, to describe expert centre management including the use of [IL1]i, to determine management consistency with the French recommendations, to describe the purpose of using advanced imaging.

3 Material and methods

3.1 Study design and participants

This is a non-RIPH (non-research involving the human person), multicentric (3 centers), inter-regional, retrospective, quantitative study.

Consecutive participants were included, if they fulfilled the following criteria: at least 18 years of age, with a diagnosis of gout from the expert center physician, for whom the follow-up in the expert center started between January 1, 2016 and June 1, 2019. They were excluded if it was a one-off advice (not for a follow-up), and if the diagnosis was not clear.

Patients were identified in one center from rheumatologists' consultation lists, then randomly included:

- Prof. Tristan PASCART for Saint-Philibert Hospital (Lille, GHICL)
- Dr. Sébastien OTTAVIANI for Bichat Hospital (Paris, APHP)
- Prof. Thomas BARDIN, Prof. Pascal RICHETTE, Prof. Frédéric LIOTE, Prof. Hang-Korng EA and Dr. Augustin LATOURTE for Lariboisière Hospital (Paris, APHP)

The first visit took place between January 1, 2016 and June 1, 2019, and was the index date. Data collection including follow-up visits, from computerized medical files, took place from January 1, 2016 to June 1, 2021.

3.2 Baseline and follow-up data

3.2.1 Data collected at M0:

- *Socio-demographic data*: age at inclusion, gender, ethnicity, socio-economic status, tobacco and wine intoxication, soda consumption, diet, physical activity,
- *Personal history of gout*: date of first flare, disease duration before M0, flare's number over the last 6 months before M0, patient's naivety (naïve status was defined as the absence of ULT prescription, from the disease beginning to M0), gout complications already present at M0 (including tophus, renal colic, chronic renal insufficiency, uratic

arthropathy),

- *Personal history*: body mass index (BMI), rheumatologic comorbidities, extra-rheumatologic comorbidities (diabetes, HTA, major cardiovascular event, congestive heart failure, dyslipidemia, liver disease),
- *Family history (1st and 2nd level)*: gout, renal colic, hyperuricemia,
- *First meeting context*: consultation or hospitalization, and referral reason if possible
- *Additional imaging prescription*: joint ultrasound and or DECT, indication, result
- *Background treatment*:
    - *hyperuricemic drugs*: antihypertensive treatment (beta-blocker other than losartan, angiotensin converting enzyme inhibitor, angiotensin II receptor antagonist), diuretic (loop or thiazide), kardegic
    - *hypouricemic drugs*: anti-hypertensive treatment (losartan or calcium channel blocker), lipid-lowering treatment, treatment of end-stage renal disease (dialysis or kidney transplant)

3.2.2 Data regularly collected during the follow up, at M0, M6, M12, M24:

- *about ULT (background therapy), before and after consultation*: drug prescription (among ALLO, FBX, Benzobromarone, Probenecide, Lesinurad, Rasburicase, Pegloticase, Dual therapy), drug dosage (mg/d), prescription consistency with the 2020 French recommendations, the reason for molecule change during de follow up or therapeutic absence if applicable
- *about symptomatic and prophylactic treatment*:
    - *for all, before and after consultation*: drug prescription (among corticosteroids, NSAIDs, Colchicine, Anakinra, Canakinumab, Bitherapy), drug dosage (mg/d), prescription consistency with the 2020 French recommendations, the reason for treatment pursuit for more than 6 months or for treatment restarting after a discontinuing period
    - *specifically, for [IL1]i*: theoretical eligibility regarding patient medical history, “temporal eligibility”, if patient fulfill EMA or EULAR criteria or for [IL1]i prescription, prescription as a flare treatment (maximum 5-day) or longer

prescription, prescription consistency with EMA and/or EULAR guidelines

- BMI (kg/m^2)
- *Biological parameters*: uricemia (mg/dL), C-reactive protein (CRP, mg/L), estimated glomerular filtration rate (eGFR, mL/min), glycosylated hemoglobin (A1C, %), total cholesterol (tC, g/L), triglycerides (TG, g/L)
- *data specifically recording at M6, M12 and M24*: "lost to follow-up" patients and ground (patient's decision, physician decision, intercurrent health problem, death), number of flares or chronic pain due to persistent synovitis until the last follow-up.

3.2.3 Data collected during the 2 years of follow up:

- *comorbidity occurrence*: diabetes, HTA, chronic renal failure, dyslipidemia, non-surgical peripheral arterial occlusive disease (PAOD), liver disease
- *major cardiovascular event occurrence*: transient or constituted ischemic stroke, surgical PAOD, acute coronary disease, venous thromboembolism (VTE)
- *patient study inclusion*, concerning imaging and/or therapeutics and/or genetic
- adverse events to the most commonly used therapies (ALLO, FBX, Colchicine), and the drug dosage while adverse event occurred.

3.3 Outcome measures

The primary outpoint was the percentage of patients with SU levels below 360µmol/l (6mg/dL), and the number of gout flares between visits, at 6 months, 1 year and 2 years after ULT introduction.

Some secondary outpoints were explored.

Patients' profile in expert centers were evaluated, completed with a sub-group analysis comparing the "lost to follow-up after M0" to the other patients' profile.

The management and its consistency with the French 2020 recommendations are described with the following terms:

- Proportion of THU prescriptions in consistency with the 2020 French

recommendations defined by: 1) prescription of ULT, 2) a target uricemia of less than 360µmol/L, 3) progressive increase in ULT doses; 4) if eGFR > 60: ALLO as first line, if eGFR between 30 and 60: ALLO or FBX as first line, if eGFR < 30: FBX as first line; high cardio-vascular risk taken into consideration; 5) prophylaxis of attacks for at least 6 months when possible to prescribe

- Proportion of prophylaxis prescriptions in line with French recommendations, defined by prescribing prophylaxis for at least 6 months when possible to prescribe
- Proportion of [IL1]i use in line with EMA and EULAR recommendations; defined for EMA as at least 3 flares in the previous 12 months, contraindication or intolerance or lack of efficacy of colchicine and NSAIDs and corticosteroids; defined for EULAR as contraindication, intolerance or lack of efficacy of colchicine, NSAIDs and corticosteroids.

Finally, the place of the different imaging techniques in the diagnosis has been observe, for diagnostic and prognostic purposes.

3.4 Statistical analysis

For the patient profile description, we performed a descriptive analysis of the data: means (standard deviation, SD) for continuous variable with normal distribution, medians (interquartile range, IQR) otherwise, minima and maxima were calculated for the quantitative variables, while numbers and frequencies were calculated for the qualitative variables. The 95% confidence intervals were calculated around the proportion of the 360µmol/L uricemia target (360-target) achieved at each visit.

In order to compare the different sub-populations, we conducted bivariate analyses: Student's t-tests (or Mann-Whitney-Wilcoxon in the absence of normality) to compare quantitative variables, and Chi-2 tests (or Fisher's exact test in case of small effective) to compare qualitative variables.

Statistical analyses were performed using R software (version 4.0.5), and were carried out by the biostatistics unit of the GHICL Clinical Research and Innovation Delegation.

3.5 Patients information and ethical considerations

This study is qualified as a research not involving the human person (RNIHP). The study protocol was submitted to the GHICL Internal Research Ethics Committee for review on 19 January 2021 (Project reference: RNIPH-2021-02).

Each patient included in the study received an information letter, specifying the nature of transmitted informations, the data recipients, the length of time the data would be kept, and a reminder of their rights. This information letter was sent by post, with acknowledgement of receipt, to included patients of the research, and accompanied by an objection form to be returned if the patient wished so.

In addition to this specific information, each patient was informed by the following sentence on their summons: "Your data may be used for medical research purposes. For further information, you can contact the Correspondant Informatique et Libertés Recherche at the following address: correspondant.recherche@ghicl.net ".

4 Results

4.1 Flowchart

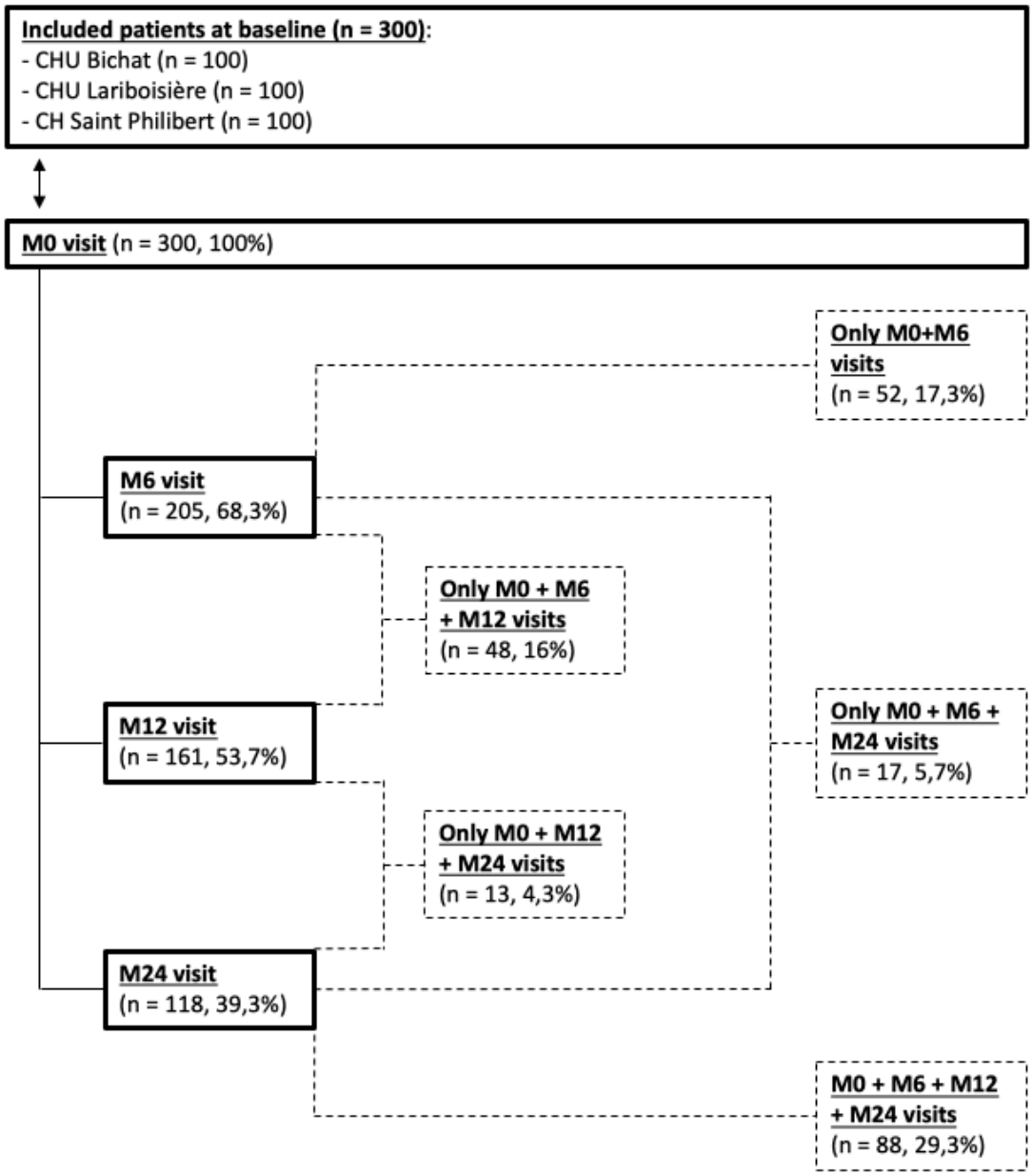


Figure 8. Study flow chart

Patients didn't all completed the four visits, but the absence to one visit didn't necessarily imply the absence to the future visits (for example, if an absence was justified by an intercurrent health problem). Thus, a patient who only visits at M0 and M6, for example, will be listed as a lost to follow-up at M12 and at M24, as the reason for not visiting may change between each visit.

4.2 Study population

Table 1. Baseline Population

Parameters	*Effective (%)*	*Mean ± SD*	*Median [Q1-Q3]*	*Min - Max*	*Missing data (n)*
Center					
• CHU Bichat	100 (33.3%)	-	-	-	0
• CHU Lariboisière	100 (33.3%)	-	-	-	0
• CH Saint-Philibert	100 (33.3%)	-	-	-	0
Humankind					0
• Women	57 (19%)	-	-	-	
• Men	243 (81%)	-	-	-	
Age at inclusion (years)	-	62.2 ± 15.2	64 [53; 74]	17 - 97	0
Ethnicity					9
• Caucasian	163 (56%)	-	-	-	
• North Africa	49 (16.8%)	-	-	-	
• Sub Saharan Africa	48 (16.5%)	-	-	-	
• South East Asia	15 (5.2%)	-	-	-	
• Middle East	2 (0,7%)	-	-	-	
• Others	14 (4.8%)	-	-	-	
BMI (kg/m^2)	-	27.9 ± 4.9	27.2 [24.8; 30.4]	13.5 - 49	53
Diet rich in purine and/or fructose	116 (47%)	-	-	-	53
Practice of regular physical exercise	31 (12.6%)	-	-	-	53
Socio-economic status					38
• Managers	14 (5.3%)	-	-	-	
• Academic profession	39 (14.9%)	-	-	-	
• Workers, farmers	35 (13.4%)	-	-	-	
• Unemployed	13 (5%)	-	-	-	
• Home keeper, or retired, or disabled	161 (61.5%)	-	-	-	
Smocking status					1
• No-smoker	190 (63.5%)	-	-	-	
• Current smoker	41 (13.7%)	-	-	-	
• Former smoker	68 (22.7%)	-	-	-	
Beverages (alcohol and/or soda)					1
• No	194 (64.9%)	-	-	-	
• Current	75 (25%)	-	-	-	
• Former	30 (10%)	-	-	-	
Hyperuricemic treatment, in patient's medical order					1
• 0	103 (34.4%)	-	-	-	
• 1	70 (23.4%)	-	-	-	
• ≥ 2	126 (42.1%)	-	-	-	
Hypouricemic treatment, in patient's medical order					1
• 0	126 (42.1%)	-	-	-	
• 1	95 (31.8%)	-	-	-	
• ≥ 2	78 (26.1%)	-	-	-	
If yes, presence of a terminal kidney failure treatment (dialysis, kidney transplant)	4 (1.3%)	-	-	-	
Personal history of other rheumatological disorders	**100 (33.4%)**				1
• Osteoarthritis	72 (72%)	-	-	-	
• Hydroxyapatite crystal disease	22 (22%)	-	-	-	
• Primary hyperparathyroidism	2 (2%)	-	-	-	
• Rheumatoid arthritis	2 (2%)	-	-	-	
• Psoriasic arthritis	4 (4%)	-	-	-	
• Others	13 (13%)	-	-	-	
of which, patients with ≥ 2 comorbidities	17 (17%)	-	-	-	
Personal gout complication at inclusion	225 (75%)	-	-	-	0
• Tophus*	144 (48%)	-	-	-	
• Renal lithiasis on imaging and or renal colic	35 (11.7%)	-	-	-	
• Chronic renal failure	128 (42.7%)	-	-	-	

• Gouty arthropathy	58 (19.3%)	-	-	-	
Personal history of other comorbidities					
• Diabetes mellitus	**84 (28.1%)**	-	-	-	1
Type 1	2 (2.4%)	-	-	-	
Type 2: non-insulin-dependent	56 (66.7%)	-	-	-	
Type 2: insulin-dependent	26 (31%)	-	-	-	
• Arterial hypertension	**181 (60.5%)**	-	-	-	1
• Cardiovascular history	**76 (25.4%)**	-	-	-	1
Cerebral stroke	17 (22.4%)	-	-	-	
Acute PAOD and/or coronaropathy	42 (55.3%)	-	-	-	
VTE	9 (11.8%)	-	-	-	
• Congestive heart failure	**38 (12.7%)**	-	-	-	1
• Dyslipidemia	**100 (33.4%)**	-	-	-	1
• Liver disease	**11 (3.7%)**	-	-	-	1
• Obesity (ie BMI > 30 kg/m^2)	**74 (24.6%)**				53
Family history of					
• Gout	**55 (18.3%)**	-	-	-	0
First degree	46 (83.6%)	-	-	-	0
Second degree	9 (16.4%)	-	-	-	0
• Renal colic	**5 (1.7%)**	-	-	-	0
• Hyperuricemia	**2 (0.7%)**	-	-	-	0
Age at diagnostic (years)	-	56 ± 17.3	58 [45; 68]	15 - 94	13
Duration of the disease before inclusion (years)	-	5.8 ± 8.6	2 [0.2; 8]	0 - 53	14
Number of gout flares over the last 6 months	-	2.1 ± 2.8	1 [1; 2]	0 - 20	18
Joint distribution at inclusion					1
• mono-articular	93 (31.1%)	-	-	-	
• oligo or poly-articular	206 (68.9%)	-	-	-	
Initial uricemia, at inclusion (mg/dL)					17
• Global	-	8.18 ± 2.37	8.15 [6.7; 9.5]	1.7 - 16.5	
• In naïve for ULT patients	-	7.25 ± 2.33	7.35 [5.5; 8.72]		
• Non-naïve for ULT patients	-	8.78 ± 2.21	8.61 [7.48; 9.9]		
Naïve for ULT					0
• No**	117 (39%)	-	-	-	
• Yes	183 (61%)	-	-	-	
If current urate lowering therapy at inclusion					0
• Allopurinol (*effective*), and posology (*mean, median, min-max*)	45 (55.6%)	173.3 ± 84.3	150 [100; 200]	50 - 300	
• Febuxostat (*effective*), and posology (*mean, median, min-max*)	34 (42%)	84.7 ± 19.1	80 [80; 80]	40 - 120	
• Benzobromarone, Probenicide	2 (2.4%)	-	-	-	
• Lesinurad	0 (0%)	-	-	-	
• Rasburicase, Pegloticase	0 (0%)	-	-	-	
• Bithérapie	0 (0%)	-	-	-	
First consultation context					0
• Consultation	190 (63.3%)	-	-	-	
• Hospitalization	110 (36.7%)	-	-	-	
If specifically referred in expert centre, reason	**178 (59.3%)**	-	-	-	0
• from primary care, for treatment initiation	9 (5.1%)	-	-	-	
• from another hospital department for gout management	140 (78.7%)	-	-	-	
• non-control at a submaximal dose of ULT***	9 (5,1%)	-	-	-	
• non-control at a maximal dose of ULT***	5 (2.8%)				
• non-control with non-referred management	1 (0.6%)	-	-	-	
• for initial hospital prescription	1 (0.6%)	-	-	-	
• already follow in the expert center for another rheumatological pathology	9 (5.1%)	-	-	-	
• from primary centre, for re-evaluation	2 (1.1%)	-	-	-	
• for personal convenience	2 (1.1%)	-	-	-	

* *clinical or ultrasound tophus*
** *anterior or actual, introduce before M0*
*** *in primary care*

A total of 300 patients were included in the study, between January 1, 2016 and June 1, 2019: 100 patients in each tertiary care center (**Table 1**).

Before inclusion, median duration of gout was 2 [0.2; 8] years, median number of gout flares over the last 6 months was 1 [1; 2], and 225 patients (75%) already had gout complications. The median uricemia at inclusion was 8.15 [6.7; 9.5] mg/dL, and 183 patients (61%) were ULT naïve. The first meeting context was a consultation for 190 (63.3%) and a hospitalization for the others. 178 (59.3%) were specifically referred in an expert center, essentially from another department of the hospital (78.7%). For those non-referred, the context was a direct consultation.

If there was a THU prescription before inclusion, regardless of the molecule, the mean uricemia at inclusion was 7.25 ± 2.33 mg/dL, and if not the mean uricemia was significantly higher with a mean of 8.78 ± 2.21 mg/dL (**Table 2**).

Table 2. Comparison of uricemia at M0 according to THU status (n = 300)

	Missing data (n)	*THU non-naive patient*	*THU naive patient*	*p-value*
n	/	117 (39%)	183 (61%)	/
M0 uricemia (mg/dL)	17	7.25 ± 2.33	8.78 ± 2.21	<0.0001
		7.35 [5.5; 8.72]	8.61 [7.48; 9.9]	

4.3 ULT management and prescription concordance with the 2020 French recommendations, and uricemia evolution under ULT

Before M0, 81 (27%) patients had a ULT, from whom 55.6% ALLO and 42% FBX (**Table 4**). At M12 and M24, around 94% patients had a ULT, from whom around 49.5% ALLO and 48% FBX. After M0, the two main reasons for no-ULT were a delayed introduction because of rheumatologist's decision (45.7%), and a persistent diagnostic doubt (10.9%). Changes in medication had a decreasing frequency during the follow-up, with 17.6% at M0, 3.4% at M12 and 2.8% at M24. The main arguments for ULT changing were variable: contraindications to current ULT for 6 (46.2%) and no control at optimal dose for 5 (38.5%) at M0, occurrence of side effects for 3 (30%) at M6, no control at optimal dose for 3 (60%) at M12, and not justified modification by another physician than the referring rheumatologist for 2 (66.7%) at M24. Compliance, defined as at least 6 intakes per week, was observed for 126 patients (84%) at M12, and for 98 patients (86.7%) at M24.

There was no-concordance between 2020 French recommendations and ULT prescription for 9 patients after the M0 visit, 5 after the M12 visit. The prescription of another molecule when ALLO was indicated as the first line therapy, concerned 5 patients at M0 and 2 patients at M6 and M12. The absence of dosage changing for a compliant patient who hadn't reached his 360-target was concerning 2 patients at M0, 2 at M12 and 2 at M24. This concordance couldn't be specified because of no SU level available for 26 (12.9%) patients at M6, 12 (7.8%) patients at M12, and 17 (14.9%) patients at M24.

Among not lost to follow-up patients, for whom SU values were available, 360-target was reached for 59.4% at M6, 67.9% at M12, and 78.6% at M24. SU level was lower than 50mg/L for 34.1% at M6, 51.1% at M12 and 51% at M24. At M6, still 30.7% experienced at least 1 gout attack and 17.1% suffered from chronic synovitis pain without a real attack, at M12 respectively 23.6% and 8.1%, and at M24 respectively 13.1% and 9.1% (**Table 4**).

Mean uricemia was 8.18 ± 2.37 mg/dL at baseline, 5.47 ± 1.85 mg/L at M12 and 5.06 ± 1.74 mg/dL (**Table 3**). M0 mean CRP was 38.8 ± 64.8 and was almost inferior to 5mg/L after M0. The evolution of other quantitative clinico-biological variables collected are detailed in **Tab.3**.

Table 3. Evolution of some quantitative clinical and biological variables

Parameters at M0 (n = 300), M6 (n = 205), M12 (n = 161) et M24 (n = 122)	*Missing data (n)*	*Mean ± SD*	*Median [Q1-Q3]*	*Min - Max*
Uricemia (mg/dL)				
• M0	17	8.18 ± 2.37	8.15 [6.7 ; 9.5]	1.7 - 1.65
• M6	35	5.99 ± 2.06	5.65 [4.6 ; 6.8]	2.54 - 1.79
• M12	24	5.47 ± 1.85	4.91 [4.2 ; 6.5]	1.9 - 11.68
• M24	24	5.06 ± 1.74	4.95 [3.9 ; 5.8]	2.0 - 11.24
CRP (mg/L)				
• M0	22	38.8 ± 64.8	4.5 [0 ; 50.8]	0 - 299
• M6	44	5.2 ± 18.7	1 [0 ; 3.5]	0 - 175
• M12	32	3.3 ± 11.5	0 [0 ; 2]	0 - 91
• M24	27	3.6 ± 9.7	1 [0 ; 2]	0 - 71
eGFR (mL/min)				
• M0	21	64.8 ± 26.7	65 [45 ; 82.8]	8.9 - 146
• M6	55	63.2 ± 26.8	62.8 [42.9 ; 83.8]	10.4 - 130
• M12	48	66.6 ± 27.7	64 [46 ; 89]	14 - 131
• M24	37	63.4 ± 26.5	64 [45 ; 84]	13.9 - 120
Glycosylated hemoglobin (%)				
• M0	249	6.7 ± 1.6	6.5 [5.8 ; 7.2]	5.1 - 14.5
• M6	192	6.3 ± 1.1	6.6 [5.7 ; 7]	3.8 - 8.1
• M12	152	5.8 ± 3.2	6.4 [5 ; 7.1]	0.8 - 10
• M24	113	6.3 ± 1.1	5.9 [5.5 ; 7.5]	5 - 8
tC (g/L)				
• M0	238	1.8 ± 0.5	1.8 [1.3 ; 2.2]	0.9 - 2.9
• M6	187	1.8 ± 0.5	1.9 [1.5 ; 2]	0.5 - 2.4
• M12	148	1.9 ± 0.3	1.9 [1.6 ; 2]	1.3 - 2.4
• M24	109	1.9 ± 0.3	1.9 [1.8 ; 2.2]	1.3 - 2.5

We have plotted the evolution of the mean SU level and CRP over the visits (**Figure 9**). The grey areas correspond to the 95% confidence interval around the mean value at each visit.

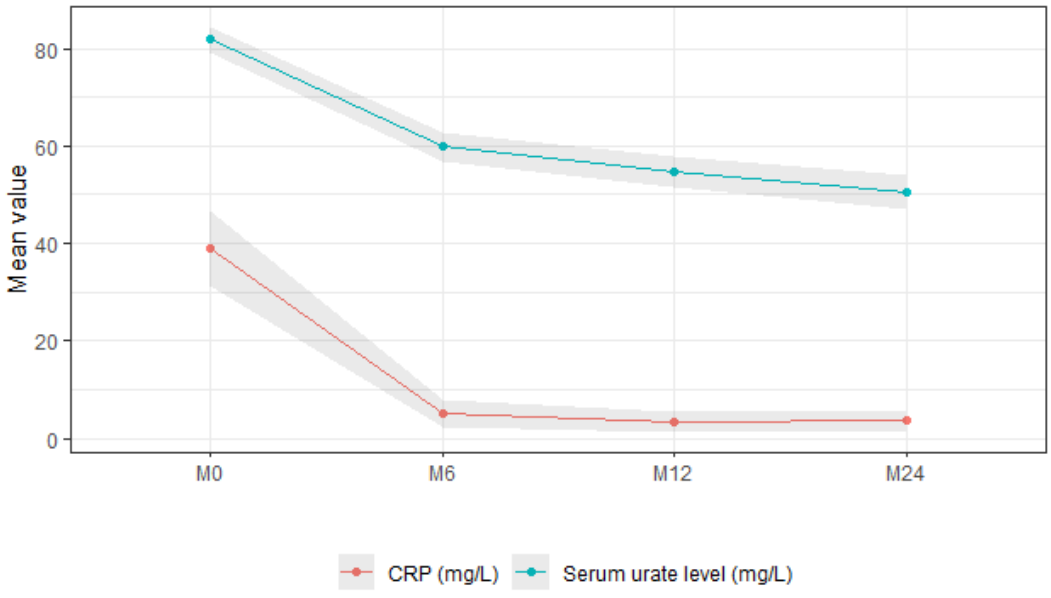


Figure 2. Evolution of SU level and C-reactive protein during the follow up, respecting SFR 2020 recommendations on the gout management.

Table 4. ULT management and results, and prescription concordance with the 2020 French recommendations (N = 300)

	M0 (N = 300)		*M6 (N = 265)*		*M12 (N = 161)*		*M24 (N = 122)*	
	*	Value	*	Value	*	Value	*	Value
Pre-consultation ULT • yes • no	0	 81 (27%) 219 (73%)	0	 188 (91.7%) 17 (8.3%)	0	 151 (93.8%) 10 (6.2%)	0	 114 (93.4%) 8 (6.6%)
If pre-consultation ULT, molecule and dosage: - **Allopurinol** • ≤ 100mg/d • 101-200mg/d • ≥ 201mg/d • mean ± SD - **Febuxostat**: • ≤ 80mg/d • 81-120mg/d • ≥ 121mg/d • mean ± SD - **Benzbromarone** - **Probenecide** - **Lesinurad** - **Rasburicase** - **Pegloticase** - **Bitherapy**	0	 **45 (55.6%)** 22 (48.9%) 12 (26.7%) 11 (24.4%) 173.3 ± 84.3 **34 (42%)** 28 (82.4%) 6 (17.6%) 0 (0%) 84.7 ± 19.1 **1 (1.2%)** **1 (1.2%)** **0 (0%)** **0 (0%)** **0 (0%)** **0 (0%)**	0	 **92 (48.9%)** 29 (31.5%) 29 (31.5%) 34 (37.0%) 208.2 ± 90.6 **91 (48.4%)** 81 (89%) 9 (9.9%) 1 (1.1%) 76.8 ± 24.1 **1 (0.5%)** **1 (0.5%)** **0 (0%)** **0 (0%)** **0 (0%)** **3 (1.6%)**	0	 **75 (49.7%)** 9 (12%) 23 (30.7%) 43 (57,3%) 260 ± 90 **72 (47.7%)** 62 (86.1%) 9 (12.5%) 1 (1.4%) 80.4 ± 29 **2 (1.3%)** **0 (0%)** **0 (0%)** **0 (0%)** **0 (0%)** **2 (1.3%)**	0	 **56 (49.1%)** 4 (7.1%) 10 (17.9%) 42 (75%) 299.1 ± 97 **55 (48.2%)** 46 (83.6%) 6 (10.9%) 3 (5.5%) 84.4 ± 33.3 **1 (0.9%)** **0 (0%)** **0 (0%)** **0 (0%)** **0 (0%)** **2 (1.8%)**
Post-consultation ULT • yes • no	0	 254 (84.7%) 46 (15.3%)	0	 201 (98%) 4 (2%)	0	 155 (96.3%) 6 (3.7%)	0	 114 (93.4%) 8 (6.6%)
If post-consultation ULT, molecule and dosage: - **Allopurinol**: • ≤ 100mg/d • 101-200mg/d • ≥ 201mg/d • mean ± SD - **Febuxostat**: • ≤ 80mg/d • 81-120mg/d • ≥ 121mg/d • mean ± SD - **Benzbromarone** - **Probenecide** - **Lesinurad** - **Rasburicase** - **Pegloticase** - **Bitherapy****	0	 **126 (49.6%)** 98 (77.8%) 17 (13.5%) 11 (8.7%) 122.1 ± 68.9 **122 (48%)** 114 (93.4%) 7 (5.7%) 1 (0.8%) 68 ± 25.6 **1 (0.4%)** **1 (0.4%)** **0 (0%)** **0 (0%)** **0 (0%)** **4 (1.6%)**		 **96 (47.8%)** 28 (29.2%) 22 (22.9%) 46 (48.0%) 229.2 ± 105.3 **99 (49.3%)** 86 (86.9%) 12 (12.1%) 1 (1%) 77.7 ± 24.2 **2 (1%)** **1 (0.5%)** **0 (0%)** **0 (0%)** **0 (0%)** **3 (1.5%)**		 **76 (49%)** 14 (18.4%) 12 (15.8%) 50 (65.8%) 275.7 ± 114.5 **75 (48.4%)** 64 (85.3%) 9 (12%) 2 (2.7%) 80.8 ± 29.9 **2 (1.3%)** **0 (0%)** **0 (0%)** **0 (0%)** **0 (0%)** **2 (1.3%)**		 **57 (50%)** 4 (7%) 8 (14%) 45 (79%) 313.5 ± 105.2 **55 (48.2%)** 44 (80%) 7 (12.7%) 4 (7.3%) 84.4 ± 36.7 **1 (0.9%)** **0 (0%)** **0 (0%)** **0 (0%)** **0 (0%)** **1 (0.9%)**
Dosage change during the visit: - No - Yes: • Side effect to current dosage • Too low SU level • Reintroduction with increasing dosage	0	 **58 (95.1%)** **3 (4.9%)** 0 (0%) 2 (66.7%) 1 (33.3%)	0	 **170 (97.1%)** **5 (2.9%)** 2 (40%) 2 (40%) 1 (20%)	0	 **132 (93.6%)** **9 (6.4%)** 1 (11.1%) 6 (66.7%) 2 (22.2%)	0	 **101 (96.2%)** **4 (3.8%)** 0 (0%) 4 (100%) 0 (0%)
Patient compliance: - yes, at least 6 times a week - no : • due to the patient (voluntarily or not) • because of side effects • stop by another physician (e.g. during a hospitalization) • medical order missing			0	 **156 (83%)** **31 (17%)** 20 (62.5%) 7 (21.9%) 2 (6.3%) 3 (9.4%)	1	 **126 (84%)** **24 (16%)** 15 (62.5%) 6 (25%) 1 (4.2%) 2 (8.3%)	1	 **98 (86.7%)** **15 (13.3%)** 10 (66 .7%) 4 (26.7%) 0 (0%) 1 (6.7%)

Concordance of ULT prescription with the 2020 French recommendations: • yes • no • not specified (no biology available)	0	 241 (94.9%) 9 (3.5%) 4 (1.6%)	0	 171 (85.1%) 4 (2%) 26 (12.9%)	1	 137 (89%) 5 (3.2%) 12 (7.8%)	0	 95 (83.3%) 2 (1.8%) 17 (14.9%)
Reason for no-concordance - first line was Allopurinol - first line was Febuxostat - consistency with previous recommendations - no respect of contraindication - no respect of recommended dosage - no dosage adaptation in a compliant patient who has not reached his 360-target - too low uricemia (<4mg/dL) for a too long time (> 6 months)	0	 5 (55.6%) 1 (11.1%) 0 (0%) 0 (0%) 1 (11.1%) 2 (22.2%) 0 (0%)	0	 2 (50%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 2 (50%) 0 (0%)		 2 (50%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 2 (50%)		 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 2 (100%) 0 (0%)
SU level at the consultation: • < 6.0 mg/dL (target) • ≥ 6.0 mg/dL • < 5.0 mg/dL • ≥ 5.0 mg/dL	17	 46 (16.3%) 237 (83.7%) 26 (9.2%) 257 (90.8%)	35	 101 (59.4%) 69 (40.6%) 58 (34.1%) 112 (65.9%)	24	 93 (67.9%) 44 (32.1%) 70 (51.1%) 67 (48.9%)	24	 77 (78.6%) 21 (21.4%) 50 (51%) 48 (49%)
Since the last consultation: • at least one flare • chronic pain because of chronic synovitis	-	 - -	0	 63 (30.7%) 35 (17.1%)	0	 38 (23.6%) 13 (8.1%)	0	 16 (13.1%) 11 (9.1%)

* missing data (n)

** Bitherapy: Allopurinol and Benzobromarone for 1 patient, Febuxostat and Benzobromarone for 2 patients, Benzobromarone and Raburicase for 1

*** Except biotherapy

4.5 Gout symptomatic treatment management and concordance with *the 2020 French recommendations* (usual treatment and [IL1]i), and flares evolution under symptomatic treatment

At baseline, in 78 (26%) cases, prophylaxis was a part of patient's background treatment, vs. 244 (81.3%) after the first consultation (**Table 5**). After M24, 28 patients (23%) still had a prophylaxis. Colchicine was the main SoC drug prescribed, and its median dosage during all the follow-up was 0.5 [0.5 ; 0.5] mg/L.

Some patients received corticosteroids at some point during follow-up. At M0, 56 (18.7%) patients had corticosteroids, of which 51 (91%) orally. At M6, 14 (6.9%) patients had corticosteroid, all in intra-articular form. Proportions at M12 and M24 are very low (**Table 5**).

Some patients received flare prophylaxis for more than 6 months. The cover of a ULT dosage modification or a poor compliance was concerning 29 (39.2%) patients at M0, 39 (32.5%) at M6, 21 (33.9%) at M12, 9 (31%) at M24. The pursuit to cover persistent flares or chronic pain on chronic synovitis without flares, was concerning 14 (22.6%) patients at M12 and 7 (24.1%) patients at M24. No discrepancies in adjuvant prescription was found, regarding French recommendations (**Table 5**).

Despite symptomatic treatment, gout flares' persistence was noticed for 63 (30.7%) patients at M6, for 38 (23.6%) at M12 and for 16 (13.1%) at M24. A chronic pain on persistent chronic synovitis was noticed for 35 (17.1%) patients at M6, 13 (8.1%) at M12 and 11 (9.1%) at M24 (**Table 5**).

Among patients presenting a flare at the M0 visit, EULAR criteria were fulfilled for 36 (12%) patients, of whom EMA criteria were fulfilled for 15 (5%) patients. A total of 46 (15.3%) finally received an [IL1]i drug, i.e. 10 patients outside the EULAR criteria. There was no canakinumab prescription (**Table 5**).

In a subgroup analysis for [IL1]i prescription at M0 (**Table 6**), the patients fulfilling EMA or EULAR official criteria to [IL1]i were respectively 11% and 26% and in Bichat, 2% and 6% in Lariboisière, 2% and 4% in Saint Philibert. Effective [IL1]i prescriptions after M0 were concerning 35% of patients in Bichat, 7% in Lariboisière and 4% in Saint Philibert.

Table 5. Gout symptomatic treatment management and concordance with the 2020 French recommendations (usual treatment and [IL1]i)

	M0 (N = 300)		*M6 (N = 265)*		*M12 (N = 161)*		*M24 (N = 122)*	
	*	Value	*	Value	*	Value	*	Value
Pre-consultation adjuvant • yes • no	0	 78 (26%) 222 (74%)	0	 147 (71.7%) 58 (28.3%)	0	 82 (50.9%) 79 (49.1%)	0	 33 (27%) 89 (73%)
If yes, molecule and dosage: - **Corticosteroids** - **AINS** - **Colchicine** - **Anakinra** - **Canakinumab** - **Bitherapy** - **Tritherapy**	0	 4 (5.1%) 2 (2.6%) 71 (91%) 0 (0%) 0 (0%) 0 (0%) 1 (1.3%)	0	 5 (3.4%) 0 (0%) 138 (93.9%) 3 (2%) 0 (0%) 0 (0%) 1 (0.7%)	0	 3 (3.7%) 1 (1.2%) 74 (90.2%) 3 (3.7%) 0 (0%) 0 (0%) 1 (1.2%)	0	 1 (3%) 2 (6.1%) 26 (78.8%) 3 (9.1%) 0 (0%) 0 (0%) 1 (3%)
Post consultation adjuvant • yes • no	0	 244 (81.3%) 56 (18.7%)	0	 123 (60%) 82 (40%)	0	 64 (39.8%) 97 (60.2%)	0	 28 (23%) 94 (77%)
If yes, molecule and dosage: - **Corticosteroids** - **AINS** - **Colchicine** *Median [Q1 ; Q3]* - **Anakinra** - **Canakinumab** - **Bitherapy** - **Tritherapy**	0	 5 (2%) 1 (0.1%) 225 (92.2%) *0.5 [0.5 ; 0.5]* 12 (4.9%) 0 (0%) 0 (0%) 1 (0.4%)	0	 5 (4.1%) 2 (1.6%) 112 (91.1%) *0.5 [0.5 ; 0.5]* 3 (2.4%) 0 (0%) 0 (0%) 1 (0.8%)	0	 3 (4.7%) 2 (3.1%) 54 (84.4%) *0.5 [0.5 ; 0.5]* 4 (6.2%) 0 (0%) 0 (0%) 1 (1.6%)	0	 1 (3.6%) 1 (3.6%) 23 (82.1%) *0.5 [0.5 ; 0.5]* 2 (7.1%) 0 (0%) 0 (0%) 1 (3.6%)
If adjuvant prescription (except [IL1]i), concordance with the French 2020 recommendations • yes • no	0	 232 (100%) 0 (0%)	1	 118 (99.2%) 0 (0%)	0	 60 (100%) 0 (0%)	0	 26 (100%) 0 (0%)
Reason for ongoing adjuvant for more than 6 months: - unspecified - persistent flares, or chronic pain on chronic synovitis without flares (1) - covering ULT dosage change, or a poor ULT compliance (2) - persistent clinical tophus or persistent uratic stock on imaging (3) - (1) and (2) - (1) and (3) - to cover an intercurrent event - gradual decrease to avoid crisis (if high initial uratic stock or high initial uricemia) - associated CPPD-rheumatism prophylaxis - Corticosteroids prescription for another indication	171	 0 (0%) 12 (16.2%) 29 (39.2%) 0 (0%) 27 (36.5%) 0 (0%) 0 (0%) 1 (1.4%) 0 (0%) 3 (4.1%)	3	 5 (4.2%) 11 (17.5%) 39 (32.5%) 18 (15%) 27 (22.5%) 2 (1.7%) 2 (1.7%) 2 (1.7%) 1 (0.8%) 3 (2.5%)	2	 2 (3.2%) 14 (22.6%) 21 (33.9%) 9 (14.5%) 11 (17.7%) 0 (0%) 0 (0%) 1 (1.6%) 1 (1.6%) 3 (4.8%)	1	 2 (6.9%) 7 (24.1%) 9 (31%) 3 (10.3%) 6 (20.7%) 0 (0%) 0 (0%) 1 (3.4%) 0 (0%) 1 (3.4%)
Corticosteroid uses within follow-up - No - Yes • Oral corticosteroids • Joint infiltration • Intravenous bolus	0	 **244 (81.3%)** **56 (18.7%)** 51 (91%) 3 (5.4%) 16 (28.6%)	1	 **190 (93.1%)** **14 (6.9%)** 0 (0%) 14 (100%) 0 (0%)	1	 **157 (98.1%)** **3 (1.9%)** 0 (0%) 3 (100%) 0 (0%)	0	 **118 (96.7%)** **4 (3.3%)** 1 (25%) 3 (75%) 0 (0%)
Patients' profile regarding [IL1]i fulfilling official criteria, among patients presenting a flare at M0 visit: • EMA criteria fulfilled • EULAR criteria fulfilled	1	 15 (5%) 36 (12%)	0	 3 (1.5%) 5 (2.4%)	2	 0 (1.2%) 5 (3.1%)	0	 3 (2.5%) 3 (2.5%)

[IL1]i prescription - No - Yes • for flare treatment (maximum 5 days) • for a longer time than flare treatment If prescription, molecule • Anakinra • Canakinumab If prescription, concordance • to EMA criteria • to EULAR criteria	0	 **254 (84.7%)** **46 (15.3%)** 33 (11%) 13 (4.3%) 46 (100%) 0 (0%) 15 (32.6%) 36 (78.3%)	0	 **200 (97.6%)** **5 (2.4%)** 1 (0.5%) 4 (2%) 5 (100%) 0 (0%) 2 (40%) 4 (80%)	0	 **154 (95.7%)** **7 (4.3%)** 2 (1.2%) 5 (3.1%) 7 (100%) 0 (0%) 2 (28.6%) 5 (71.4%)	0	 **119 (97.6%)** **3 (2.4%)** 1 (0.8%) 2 (1.6%) 3 (100%) 0 (0%) 2 (100%) 3 (100%)

* missing data
** modifications during the follow up due to losses of follow up patients
Abbreviations: CPPD = Calcium Pyrophosphate Deposition

Table 6. Subgroup analysis of [IL1]i prescription, at M0 (N = 300)

	Missing data (n)	*Saint Philibert (n=100)*	*Bichat (n=100)*	*Lariboisière (n=100)*
Fulfilling EMA official criteria for [IL1]i	0	2 (2%)	11 (11%)	2 (2%)
Fulfilling EULAR official criteria for [IL1]i	0	4 (4%)	26 (26%)	6 (6%)
[IL1]i prescription at M0 - **No** - **Yes** • for flare treatment (maximum 5 days) • for a longer time than flare treatment	0	 **96 (96%)** **4 (4%)** 1 (1%) 3 (3%)	 **65 (65%)** **35 (35%)** 26 (26%) 9 (9%)	 **93 (93%)** **7 (7%)** 6 (6%) 1 (1%)
If [IL1]i prescription, molecule • Anakinra • Canakinumab	0	 4 (100%) 0 (0%)	 35 (100%) 0 (0%)	 7 (100%) 0 (0%)

4.6 Place of the different imaging techniques in the diagnosis and other uses

60% of patients included in our study had at least one advanced imaging test during the follow-up period (**Table 7a**). For 81 (45%) patients, it consisted of both a joint ultrasound and a DECT. The relevant indication to perform those were for diagnostic purposes only for 88 (48.9%) patients, to evaluate urate load only for 69 (38.3%) patients, and for both in 12.8% of cases.

Among joint ultrasounds performed, 136 (79.5%) patients were presenting at least one gout sign, of which 41 (24%) had double contour sign only, 39 (22.8%) had tophus only, and 56 (32.7%) had both. Among DECT performed, 59 (67.8%) had MSU crystal deposition.

36 (20%) of those patients that had undergone an advanced imaging scan were included in an imaging study, and 31 (34.4%) of those that had undergone a DECT.

Table 7a. The place of the different imaging techniques, and the correlation with the fact of being included in a study.

	Missing data	*Effective (%)*
Advanced imaging test performed at M0 in including population (N = 300): - Yes : • Joint ultrasound only • DECT only • Both - No : • No medical prescription • Prescribed but not carried out because the patient was lost to follow-up	0	**180 (60%)** 90 (50%) 9 (5%) 81 (45%) **120 (40%)** 119 (99.2%) 1 (0.8%)
If an advanced imaging test was performed, the relevant indication was (N = 180): • To evaluate uratic load only • For diagnostic purposes only • Both	0	69 (38.3%) 88 (48.9%) 23 (12.8%)
Joint ultrasoud results (N = 171) : • No gout evidence • Double contour sign only • Tophus only • Both double contour sign and tophus	0	35 (20.5%) 41 (24%) 39 (22.8%) 56 (32.7%)
DECT results (N = 90) : • negative for MSU deposition • positive for MSU deposition	3	28 (32.2%) 59 (67.8%)
Participation to an imaging study during the 2 years of follow-up, among patients who benefited of an advanced imaging test: • Yes • No	0	36 (20%) 144 (80%)

45 patients (15%) were included in a study at M0, of which 27 patients to an imaging study (60%), 9 patients to a genetic study (20%), and both for 9 patients (20%) (**Table 7b**).

Table 7b. Study participation during the two years of follow up

	Missing data (n)	Effective (%)
Study participation during the two years of follow up • Yes • No If yes, type*: • Imaging study • Therapeutic study • Genetic study	0	 45 (15%) 255 (85%) 36 (80%) 0 (0%) 18 (40%)

4.7 "Lost to follow-up" patients' profile

Some patients were lost to follow-up after their first consultation, despite a planned follow-up visit with their rheumatologist in the expert centre. Among them, 32 (48.5%) had been first met in an outpatient visit, and 34 (51.5%) had been met during an inpatient hospitalized care. Their mean age at inclusion was 63.6 ± 13.4 years, and the median duration of disease progression before inclusion was 1 [0 ; 5] years. The median number of gout flares over the last 6 months before inclusion was 1 [1 ; 2], the mean uricemia was 8.09 ± 2.54 mg/dL, and the mean number of gout complications already present before M0 was 1 ± 0.8 (**Table 8**).

Among the included patients, some were unable to attend all follow-up visits. The absence to a follow-up visit didn't predicted the absence to subsequent visits, as this absence was may due to an intercurrent event. 95 (31.7%) didn't go to M6 consultation, 139 (46.3%) didn't go to M12 consultation, and 178 (59.3%) didn't go to M24 consultation.

The reasons to discontinue follow-up were patient's decision, a voluntary non-recall from the rheumatologist (patient referred to his GP, once the disease is balanced), an intercurrent health problem, or patient's death. It was unknown for more than half of the patients at each visit between M6 and M24 (**Table 9**).

Table 8. M0 lost to follow up patients (only M0 consultation performed) (N = 66)

M0 lost to follow up patients (N = 66)	*Missing data (n)*	*Effective (%)*	*Mean ± SD*	*Median [Q1-Q3]*
M0 meeting context (%) • consultation • hospitalization	0	 32 (48.5%) 34 (51.5%)	 - -	 - -
Age at inclusion (years)	0	-	63.6 ± 13.4	64 [57.2 ; 72.8]
Age at gout diagnosis (years)	13	-	59.7 ± 15.5	61 [51 ; 69]
Duration of disease before inclusion (years)	14	-	4.2 ± 6.6	1 [0 ; 5]
Gout flares over the last 6 months before inclusion (n)	18	-	1.9 ± 2.4	1 [1 ; 2]
M0 uricemia (mg/L)	17	-	8.09 ± 2.54	7.92 [6.56 ; 9.45]
Gout complications already present before M0 (n)	0	-	1 ± 0.8	1 [0 ; 2]
Number of extra-rheumatologic comorbidities	1	-	1.8 ± 1.5	2 [1 ; 2]
ULT prescribed at the end of the M0 consultation: • Allopurinol • Febuxostat	0	57 (86.4%) 24 (42.9%) 32 (57.1%)	- - -	- - -

Table 9. M6, M12 and M24 lost to follow up patients' (at least M0 and another consultation performed) (N = 265)

	M6 (N = 265)		M12 (N = 161)		M24 (N = 122)	
	Missing data (n)	Effective (%)	Missing data (n)	Effective (%)	Missing data (n)	Effective (%)
Visit status - honored - non-honoured • CH Saint Philibert • CHU Bichat • CHU Lariboisière	0	 **205** (68.3%) **95** (31.7%) 14 (14.7%) 47 (49.5%) 34 (35.8%)	0	 **161** (53.7%) **139** (46.3%) 37 (26.6%) 60 (43.1%) 42 (30.2%)	0	 **122** (40.7%) **178** (59.3%) 52 (29.2%) 78 (43.8%) 48 (27.0%)
If non-honoured, reason: - unknown - patient's decision - voluntary non-recall from the rheumatologist - intercurrent health problem - death	0	 62 (65.3%) 10 (10.5%) 11 (11.6%) 12 (12.6%) 0 (0%)	0	 79 (56.8%) 10 (7.2%) 27 (19.4%) 23 (16.5%) 0 (0%)	0	 114 (64%) 12 (6.7%) 25 (14%) 24 (13.5%) 3 (1.7%)

5 Discussion

5.1 Main findings of the study

5.1.1 Key results

The main objective of our study was to evaluate the proportion of patients with SU levels below 360µmol/l (6.0mg/dL), and the number of gout attacks, 6 months, 1 year and 2 years after the management beginning. Thus, the aim was to highlight the effectiveness of the gout management proposed by the expert centres physicians.

Among the non-losses to follow-up, 360-target was reached for 59.4% at M6, 67.9% at M12, and 78.6% at M24 (**Table 3**). If we compare with other studies, in GOSPEL cohort (primary care) only 34.5% of patients treated with ALLO reached the target uricemia at the first visit [49]. In CACTUS cohort (primary care), 94% of patients were at the SU level target of 60 mg/L and 84% were below 50mg/L with a median ALLO dosage of 400 mg/day, at the end of the 1-year follow-up [57]. 2012 American data, from a survey on approximately 850 general practionners, show that care was consistent with the recommendations in only 3% of gout associated with renal disease, and 17% of tophaceous gout, including initiating a ULT at the appropriate dose with dosing titration to a SU level of 6.0 mg/dl [43]. Those US GPs are now questioning the value of the management proposed by other rheumatologic societies, and even questioning the need to reduce uric acid levels to cure gout. These claims are contradicted by the results of our study, in favour of the relevance of the French recommendations.

Our results are overall much better than in previous studies in primary care, and it is interesting to notice that more than 50% of those who reached the objective of SU level < 6.0 mg/dL, have a SU level < 5.0 mg/dL (**Table 2**).

At M6, still 30.7% had at least 1 gout attack and 17.1% suffered from chronic synovitis pain without a real attack, at M12 respectively 23.6% and 8.1%, and at M24 respectively 13.1% and 9.1% (**Table 4**). This indicates that a significant number of patients had prolonged inflammatory symptoms.

5.1.2 About baseline patient's profile and initial management: comparison with primary care cohorts

Very few patients had a ULT before inclusion: this shows that for most of the patients initiating follow-up in an expert centre, the matter was to introduce or reintroduce a ULT, rather than incrementing with unconventional therapies (e.g. uricosurics), or dual-therapies.

For this part, we have chosen to compare data from our URATE-CHALLENGE cohort (**Table 1**), to the GOSPEL and the CACTUS primary care cohorts (**Table 10**). Cardiovascular comorbidities were slightly higher in our cohort, but overall the populations of these different cohorts were comparable. Uricemia at inclusion was slightly lower in our cohort, may be due to the inflammatory syndrome presented by a lot of patients at M0, which may have distorted the values. Concerning gout complications, tophi proportion was significantly higher in our study, implying that the patients in our cohort probably had a higher uratic load. Chronic renal failure proportion were similar in the GOSPEL and URATE-CHALLENGE cohort, and very lower in the CACTUS cohort.

Table 10. Comparison with primary care cohorts

Parameters	GOSPEL [2] 2012 French cohort Age ≥ 18 years Primary Care Multicenter observational analysis	CACTUS [57] 2015 French and Greek cohorts Age ≥ 21 years Primary care Multicenter observational analysis	URATE-CHALLENGE 2021 French cohort Age ≥ 18 years 3 expert centres Multicenter observational analysis
n	1003	3079	300
Proportion of male	**87.6%**	82.6%	81%
Mean age at inclusion (y)	62.6 ± 11.4	63	62.2 ± 15.2
BMI (kg/cm^2)	28.4 ± 4.1	29.3 ± 4.7	27.9 ± 4.9
Family history of gout - global - first degree - second degree	 - 16% -	 35.3 % - -	 18.3% 15.3% 3%
Active smoker	-	28%	13.7%
Alcohol consumption >2 glasses/day	-	44%	22.7%
Used to drink more than one glass/day of non-diet sodas	-	14%	6.6%
Hypertension	54.5%	68%	60.5%
Dyslipidemia: - global - hypercholesterolemia - hypertriglyceridemia	 47.2% - -	 - 59% 39.8%	 33.4% - -
Diabetes mellitus - global	 14.9%	 -	 28.1%

- type 1 - type 2	- -	- 24.2%	- -
Congestive heart failure	-	6.4%	12.7
Arteriopathy: - Ischemic heart disease/ myocardial infarction - coronary artery disease - global	 4.3% 8.8% 13.1%	 10.1% - -	 - - 14%
Obesity - global - male - female	 - 28.1% 12.4%	 48% - -	 24.6% - -
Disease duration at inclusion, since the diagnostic (years)	8.0 ± 8.3	**5.2 ± 6.1**	5.8 ± 8.6
Age at diagnosis (y)	54.4 ± 12.9	-	56 ± 17.3
Uricemia at inclusion (mean, mg/dL)	10.05	8.7	**8.18 ± 2.37**
Number of attacks during: - the previous 12 months - the previous 6 months	 1.9 ± 1.5 -	 1.9 ± 1.5 -	 - 2.1 ± 2.8
Joint manifestations at baseline: - monoarthritis - oligoarthritis or polyarthritis	 90.9% 0.9%	 - -	 **31.1%** **68.9%**
Radiological evidence of arthropathy	51.8%	-	**19.3%**
Chronic renal failure (GFR < 60 ml/min)	43%	**8.6%**	42.7%
Tophi at inclusion	20.2%	11%	**48%**
Uric lithiasis	-	8.3%	**11.7%**
ULT at inclusion	-	81.5%	27%
ULT after M0 consultation - Allopurinol - Febuxostat	 - -	98% 11.7% 87.3%	84.7% 49.6% 48%
Compliance after M0: - to Febuxostat - to Allopurinol - global to THU	 - - -	 92% 82% -	 - - 83%
Prophylactic drug after M0 - Colchicine - NSAID - Corticosteroids - Other prophylactic drug	 - - - - -	 65.5% 92% 11.2% 0.4% 0.8%	 81.3% 92.2% 0.1% 2% 4.9%

5.1.3 About ULT management

Data show that all the patients for whom a ULT was already introduce before the follow-up in the expert centre, had very low treatment dosage (in particular for ALLO) and high uricemia, whether or not they were ULT naïve (**Table 4**).

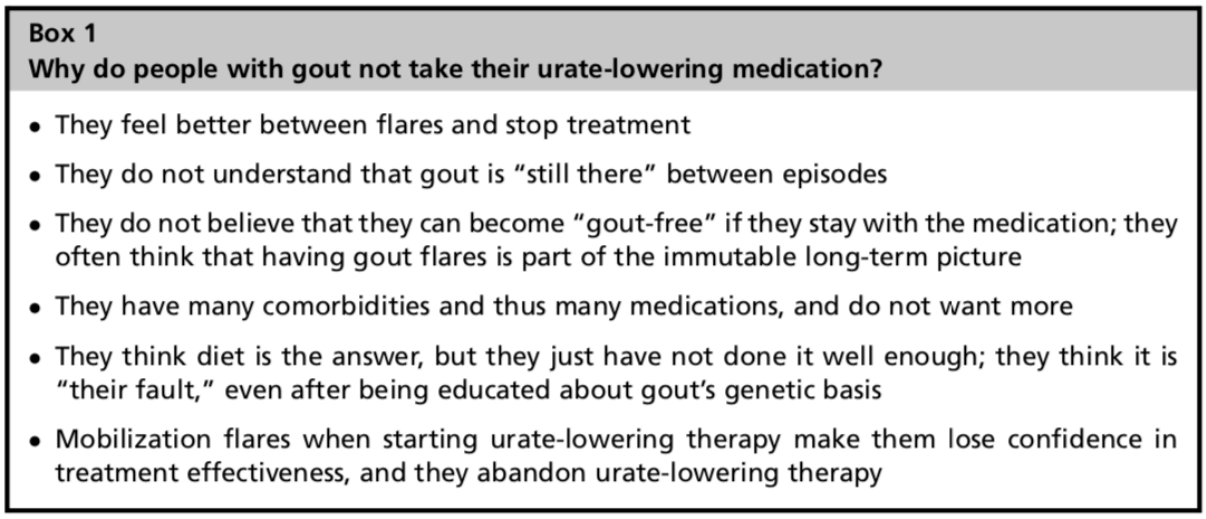
In our study, during the follow-up the ULT was most often not changed (**Table 4**), but dosage was increased. It shows that most of the patients are eligible to conventional treatments, but that the titration is not correctly performed, as it was already describe in previous studies [26,50]. Thanks to this T2T strategy and time devoted to patient education (even if not recorded), SU level evolution is satisfying with almost 80% of patients at the 360-target at 2-year of follow-up (**Table 3**).

This number is not perfect, maybe for several reasons. First, because of compliance difficulties. Secondly, because in a significant proportion of patients, the ULT introduction was delayed. Most often, the reason was a flare still in a resolution process. In smaller proportions, the reasons were for example frequent residence changes, making it difficult to closely monitor the ULT initiation (e.g. return to the country of origin for several months), or the HLA B58*01 screening. When the ULT prescription was delayed, and in parallel the patient had no longer flares under symptomatic treatment, he wasn't necessarily motivated to have a follow up. This raises questions about the timing between flare and ULT introduction. Indeed, a recent study showed that allopurinol initiation during an acute gout flare did not significantly influence daily pain, attack recurrence or inflammatory markers [60].

The concordance of THU prescribing, with French recommendations, tends to decrease during the follow-up (**Table 4**), mainly because of missing data and not because of prescribing errors. The main reason for non-concordance was the non-respect of first-line molecule as proposed in the French recommendations of 2020. This can probably be explained in part by the experience of rheumatologists with some therapies more than others, which eventually arose during discussions during the elaboration of the French recommendations.

In our study, THU compliance is quite good but doesn't improve during follow-up consultations, and is distorted by the fact that among those lost to follow-up there are probably a large number of non-compliant patients (**Table 4**). Therapeutic education hasn't been collected, because the data was rarely mentioned in patients'

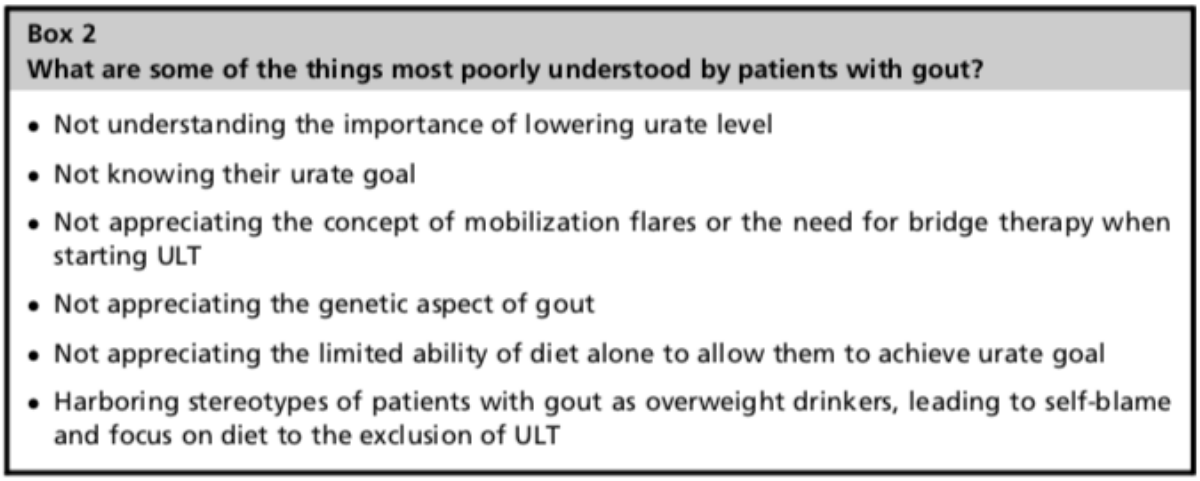
files, even though it was probably done during the consultation. As Doherty and Fields recently recalled, the compliance is essential in the objective achievement [26,54]. In his study, Fiels recalled the various reasons of non-observance and various solutions to optimize the therapeutic education of patients (**Figure 10-12**).



Box 1
Why do people with gout not take their urate-lowering medication?

- They feel better between flares and stop treatment
- They do not understand that gout is "still there" between episodes
- They do not believe that they can become "gout-free" if they stay with the medication; they often think that having gout flares is part of the immutable long-term picture
- They have many comorbidities and thus many medications, and do not want more
- They think diet is the answer, but they just have not done it well enough; they think it is "their fault," even after being educated about gout's genetic basis
- Mobilization flares when starting urate-lowering therapy make them lose confidence in treatment effectiveness, and they abandon urate-lowering therapy

Figure 10. Major reasons for the high degree of nonadherence to urate-lowering therapy (ULT) [54]



Box 2
What are some of the things most poorly understood by patients with gout?

- Not understanding the importance of lowering urate level
- Not knowing their urate goal
- Not appreciating the concept of mobilization flares or the need for bridge therapy when starting ULT
- Not appreciating the genetic aspect of gout
- Not appreciating the limited ability of diet alone to allow them to achieve urate goal
- Harboring stereotypes of patients with gout as overweight drinkers, leading to self-blame and focus on diet to the exclusion of ULT

Figure 11. Important knowledge gaps that prevent patients from having needed discussions with their physician and cause them to avoid or abandon ULT [54]

Box 3
Strategies for gout management in different rheumatology practice settings

- Small practice
  - Nurse/nurse practitioner/physician assistant most likely as educator and monitor of adherence to therapy
  - Nurse practitioner or physician assistant can follow algorithm and manage ULT titration
  - Consider text-messaging or telephone monitoring of adherence versus electronic medical record messaging
  - Consider such strategies as questionnaires, to identify patients least likely to adhere to regimen
- Group multispecialty practice that includes a rheumatologist
  - Nurse/nurse practitioner/physician assistant most likely, but could consider hiring pharmacist; could consider multidisciplinary approach
  - Consider text-messaging or telephone monitoring of adherence versus electronic medical record messaging
  - Rheumatologist educates internists (to treat-to-target and about importance of educating patients with gout) and is available for refractory cases
- Large academic practice
  - Pharmacist or nurse patient education, or team approach including social worker
  - Pharmacist or nurse monitoring (text/email or telephone, electronic medical record messaging)
  - Pharmacist can use algorithm for dose adjustment
  - Patient support groups and/or community programs
  - Consider text-messaging or telephone monitoring of adherence
- Skilled nursing facility or outpatient practice focused on elderly
  - Pharmacist or nurse educator skilled in special problems with hearing/memory
  - Closer monitoring regarding changes in eGFR and compliance
  - Monitoring for infection masquerading as gout flare
- Consultation service seeing in-patient gout
  - At discharge, have ULT plan in discharge summary
  - If volume sufficient, train nurse for postdischarge education

Figure 12. Practice setting and resources to mobilize for gout patient education and monitoring [54]

5.1.4 About symptomatic therapy management and [IL1]i prescription

A rapid relief of inflammation is one of the management goals [45].

Regarding the SoC treatments, i.e. NSAIDs, colchicine and systemic corticosteroids, the most prescribed in our study is colchicine as recommended in the French recommendations. We note that after M0, the percentage of prophylactic treatment prescription (81.3%, **Table 5**) is close to the percentage of ULT prescription (84.7%, **Table 3**), indicating compliance with the recommendation of symptomatic treatment for at least the first 6 months of ULT introduction. However, there is still a high proportion of patients under adjuvant therapy at M24 (**Table 5**), reflecting the difficulty in eradicating the chronic local inflammation caused by the crystals presence.

Corticosteroid therapy appears to be useful as an adjunct at the beginning of treatment when the burden of urate is still being lifted (**Table 5**). Its use for short periods allow to less exposure to the side effects of corticosteroids.

In the 'DTT' gout, there is a place for [IL1]i. The rationale refers to the principal mechanism of crystal induced inflammation: inflammasome activation induce IL1 production [61]. In our study, prescriptions were largely made within the Bichat hospital, but in correlation with a larger number of eligible patients (**Table 6**).

We noticed numerous off-label prescriptions, re-highlighting the difficulties with recommendation restrictions. The relevant reasons were to allow ULT introduction immediately after hospitalization for a disabled flare (a few days of [IL1]i, followed by introduction of colchicine and THU) - this conduct was motivated by difficult social contexts in most cases, and in very inflammatory flares in patients with moderate to severe chronic kidney failure in order to avoid colchicine prescription.

A 2019 study on the French GOSPEL cohort, tried to determine the proportion of patients presenting with DTT gout flares eligible to [IL1]i according to EULAR and European Social Protection Comittee definitions [52]. One fifth of patients were eligible for [IL1]i, i.e. 2 times more than in our cohort: this should be tempered, as misuse of colchicine was accounted for up to 10% of patients in this cohort [52] (**Table 11**).

Table 11. [IL1]i eligibility in different cohorts

Parameters	**GOSPEL**[1] 2019 French cohort Primary Care Multicenter observational analysis	**URATE-CHALLENGE** 2021 French cohort 3 expert centres Multicenter observational analysis
n	1003	300
Patients having contraindications or intolerance to all standard of care treatments of flares	1.9%	11.3%
Patients with possible eligibility for IL-1 inhibition, due to precautions of use for SoC	21.7%	-
Patients presenting a flare that were eligible to second-line interleukin-1 inhibition	114 (23.4%), in which only nine respecting European recommendations	7.4%

A second finding is that 100% of patients were having anakinra, used most often less than 6 months, whereas only canakinumab has a MA (**Table 5**). Canakinumab hasn't been prescribed, because in view of a very prolonged half-life and a very high cost, other therapeutic options were considered (although its indication was sometimes discussed in a multidisciplinary consultation meeting). Large randomized studies are currently available for canakinumab, but there is a real gap for anakinra. In 2013, a French retrospective study of 40 patients with baseline profiles comparable to our study, apart from the gout complications already present (tophi in 79%, arthropathy in 92%), investigated the efficacy and safety of different treatment durations (3 days, < 15 days, > 15 days) [62]. Overall, a good response to anakinra was found in more than 90% of cases, the absence of relapse in patients with prolonged treatment, and complications, mainly of an infectious nature, only in cases of prolonged treatment. Another more recent randomized non-inferiority trial published in 2019, compared anakinra versus placebo in 88 patients in which 43 with effective anakinra treatment [53]. They concluded to anakinra non-inferiority to SoC, and to a greater pain-relieving effect of anakinra versus placebo. A very recent randomized phase 2 study on 165 patients, published In august 2021, compared anakinra (at 100mg/d and 200mg/d) to triamcinolone, regarding efficacy and safety in the treatment of gout flare [63]. This cohort was comparable to ours, except that the patients were probably more inflammatory with about 4.5 flare-ups in the last year. It was concluded that anakinra was not superior to triamcinolone in this study but showed a substantial and similar reduction in patient-assessed pain, and most secondary outcomes favored anakinra. 100 and 200mg/d of anakinra had comparable efficacy.

Those studies comfort that anakinra can be considered as an effective option in

the treatment of gout flares when conventional therapy is unsuitable. Those studies are all in favor of a MA for Kineret. As French recommendations are unclear on [IL1]I indications, it would be interesting to discuss, in particular, on the duration of use, dosage and broader indications.

5.1.5 About imaging techniques

In our study, imaging tests were reported only around the inclusion period. Those were performed most often for diagnostic purposes (**Table 7a**). However, in the context of patients included in imaging studies (**Table 7b**), many DECT were also performed to quantify the uratic charge. Patients followed up in expert centres therefore potentially benefited from more imaging examinations than those managed in liberal and primary care practices, and which exceed the SFR recommendations.

5.1.6 About losses to-follow up patients' profiles

We noticed 2 categories of lost to follow-up patients: a high proportion immediately after M0 (**Table 8**), and the others later in the follow-up (**Table 9**).

For those lost to follow-up after M0 (**Table 8**), gout duration was about 1 year, therefore very recently diagnosed gouts, with a median of one attack in the last 6 months. Among those later lost to follow-up (**Table 9**), several reasons can be found: asymptomatic patients undergoing prophylactic treatment, patients with usual compliance difficulties, intercurrent health events, rheumatologist decision to stop the expert centre follow-up, patients with cognitive disorders, and finally there is a probable bias due to the COVID-19 pandemic in the second part of the follow-up.

Gout patients' follow-up is known to be difficult, due to frequent lack in patients' compliance. Therapeutic education should therefore probably be carried out very insistently from the beginning of follow-up, to enable better adherence to the drug treatment and follow-up consultations [64]. Expert centers can correct errors in management, but as gout is such a frequent pathology, primary care physicians have to know how to manage it. They have much greater rapid consultation capacity than in hospital, and can therefore afford to perform very close follow-up outside of hospital consultations, which promotes adherence.

5.2 Clinical and therapeutic implications, perspectives

The hyperuricaemia degree is a strong predictor of the occurrence of gout attacks, and persistent hyperuricaemia is closely related to the recurrence of acute attacks and the development of gout complications including death [3]. So that, the aim in future years is to do better than 80% of 360-target patients after a 2-year follow-up.

A solution to be discussed would perhaps be an earlier introduction of ULT, in order to avoid the numerous losses of follow up. This could be facilitated by the wider administration of [IL1]i at M0 in order to avoid the recurrence of flares during the introduction of ULT in patients with a high uratic load. The other interest in the wider use of [IL1]i at M0 is corroborated by the fact that after M24, 28 patients (23%) still had SoC adjuvant, as the major inflammation for some gout patients is difficult to control, with sometimes a decrease in the frequency of gout flares after only 1 year of treatment [26].

Concerning the SU target, authors showed that the lower uricemia is, the faster tophi size decrease [30]. Thus, democratizing the DECT could be useful to define a personalized uricemia target according to uratic load, the fact that the presence of clinical tophus and the articular ultrasound only give a very rough idea of the exact uratic load [65].

Regarding the compliance difficulties that affect a proportion of those lost to follow-up and almost 20% of those not lost to follow-up, there is a potential interest in developing the town-hospital link with informed staff in primary care is to allow more regular consultations (1 per month at the beginning for example, vs. 1 every 6 months in hospital) to encourage patient compliance. As it was noted in a center of our study, this education could also be enhanced by a day hospitalization devoted to the initiation of the treatment and the screening of comorbidities, like the therapeutic education by dedicated nurses, as it's done for inflammatory rheumatism under biotherapy – yet this is not feasible for all gout patients [54].

5.3 Strengths and limitations of the study

One of the strengths of our study is its multicentric character, allowing a study with a large number of different profiles. In addition, the study involved a cohort of 300 patients, that give power for statistical analysis. As our cohort seems to be comparable to the ones in primary care, our results probably generalizable to primary care management.

This study has also several limitations. First, there is the inherent limitations of retrospective observational studies, with missing data and incomplete follow-up: this loss of data is very significant in our study, and must temper the good scores for the proportion of patients on target and for compliance. Secondly, the fact that a number of patients were included in studies probably altered the number of imaging procedures performed, patient compliance, and treatment increment choices. Third, therapy education was not collected as it was not reported in the medical reports, although it is an essential part of the management. Fourth, cognitive issues, that haven't been collected in our study, may make education and monitoring more difficult.

Fourth, the fact that the collection period is very short: this does not allow time for patients to experiment with biotherapies or less conventional therapies, on which we still need efficacy data.

6 Conclusion

Patients treated in expert centres have more comorbidities, particularly cardiovascular ones, but they have overall the same baseline profiles as patients treated in outpatient settings. Apart from the rare use of [IL1]i, physicians from expert centers basically apply recommendations and use conventional treatments (of flares and ULTs) for their patients. Our conclusions on management in expert centres are therefore applicable to the expected results of management in primary care.

Our results show that the 2020 French recommendations were already being applied in referral centers prior to their publication. They allow most patients to be at 360-target at 1 and 2 years of follow-up, under standard therapies. We therefore conclude that the management currently proposed by the French recommendations is very effective. Moreover, as most of them are at 360-target under conventional ULT, gout can be adequately and completely managed in primary care.

Even with expert center follow-up, there is still a significant part of poor compliance, although largely reduced compared to what is observed in usual care. That hence the need to strengthen the city hospital network, and on the other hand to discuss an earlier introduction of ULTs, and to secure some time dedicated to patient information/education. Moreover, unlike in general practice where patients always come back, in our study there is a large number of people who are lost to follow-up.

The use of [IL1]i in expert centres is not uncommon, but the recommendations are often outdated in terms of the indications selected, due to their very restrictive nature. On the other hand, the most prescribed molecule is the one that does not have the marketing authorization. Clearer recommendations in this area are needed, and the obtaining of MA for anakinra in gout could facilitate the clarification of these recommendations.

Concerning the use of gout advanced imaging tests, DECT and US are largely used in French referral centers both for diagnostic and management purposes, although this finding is certainly biased by the specific expertise on gout advanced imaging techniques in French referral centers.

Deuxième article en Anglais
URATE CHALLENGE 2

Predictive factors associated with outcomes of gout management in referral centers

1 Abstract

Objective: gout is poorly managed in primary care, due to a lack of adherence to recommendations. Factors associated with better outcomes, when recommendations are followed, need to be identified. The main objective were to describe predictive factors to reach the 360µmol/L (6.0mg/dL) uricemia target (360-target) in French referral centers. The second objectives were to compare Allopurinol (ALLO) and Febuxostat (FBX) population, to describe ULT tolerance, and to learn about the 360-target extra-rheumatologic effects.

Method: We have first set up a bivariate generalized mixed model, to investigate the relationship between 360-target achievement at each visit and an explanatory variable of interest (fixed effect). Then we set up a multivariate generalized mixed model, using the explanatory variables that had a p-value < 0.2 in the bivariate analyses.

Results: The bivariate analysis contain four predictive factors: age at gout onset and age at follow-up starting (OR = 1.03 [1.01-1.06]), the presence of a tophus on joint ultrasound (OR = 2.63 [1.20; 5.74]), compliance with ULT when arriving to the consultation (OR = 35.36 [5.46; 229.08]), ALLO prescription > 200 mg/d before consultation (OR = 3.01 [1.21-7.47]).
The complete-model contains 3 explanatory variables: presence of tophus on joint ultrasound (OR = 3.07 [1.08; 8.69]), age (increased by one year) (OR = 1.05 [1.01; 1.09]), prescription of ALLO at a dosage > 200mg/d vs. no prescription (OR = 6.57 [1.58; 27.3]). The compliance is not present in the final model, despite its high significance in the bivariate analysis, due to the unevenness of the distribution. ALLO and FBX were comparable in terms of efficacy and safety.

Conclusion: In referral centers where gout management is optimized, some factors are significantly associated with an outcome: compliance, older age, high crystal burden at baseline, and ALLO final dosage.

2 Introduction

Gout is the most common inflammatory arthritis in men over 40 years old [9]. There are actually numerous lacks in gout management in usual care, both in primary care and rheumatology settings. Gout management suffers both from a lack of knowledge on the disease management by physicians and a poor treatment compliance.

In primary care, the absence of titration or even the discontinuation of XOI are not uncommon [9]. The over-developed fear of side effects is commonly reported to explain the underuse of ULT. Gout referral centres provide optimized gout management allowing for outcomes to be reached in a majority of patients – but not all. Predicting factors of good response to optimal management in referral centres still need to be identified.

Concerning ALLO prescription, a recent publication highlighted some difficulties with its titration [9]. The main reason is the fear of cutaneous adverse events including the feared severe cutaneous adverse reactions (SCARs), that might be observed in 2-5% of patients, directly correlated with renal function and a high initial dose of ALLO (superior to 100mg/d). Specifically concerning DRESS syndrome, some risk factors have already been identified, as an increased risk in populations of Asian and African origin and if presence of HLA B58*01 presence. *Concerning FBX difficulties of prescription*, its use in patients with a history of severe cardiovascular disease has recently been discouraged. As highlighted in SFR recommendations [29] and CARES trial [66,67], an increased mortality rate versus ALLO, and an increased risk of cardiovascular events if suddenly stopped have been observed.

The extra rheumatologic consequences of reaching the 360-target are not yet well known, especially whether it could provide cardiovascular protection and/or renal improvements. Indeed, a recent Swedish study in patients with incidental gout, without ULT, and no history of chronic heart failure or acute coronary syndrome, shows a relative risk of overall mortality of 1.08 and cardiovascular mortality of 1.20 [35].

The main objective were to describe predictive factors to reach the 360µmol/L (6.0mg/dL) uricemia target (360-target) in French referral centers. The second objectives were to compare ALLO and FBX population, to describe ULT tolerance, and to learn about the 360-target extra-rheumatologic effects.

3 Material and methods

3.1 Study design and participants

This is a non-RIPH (non-research involving the human person), multicentric (3 centers), inter-regional, retrospective, quantitative study.

Consecutive participants were included if they fulfilled the following criteria: at least 18 years of age, with a diagnosis of gout from the expert center physician, for whom the follow-up in the expert center started between January 1, 2016 and June 1, 2019. They were excluded if it was a one-off advice (not for a follow-up), and if the diagnosis was not clear.

Patients were identified in one center from rheumatologists' consultation lists, then randomly included:

- Prof. Tristan PASCART for Saint-Philibert Hospital (Lille, GHICL)
- Dr. Sébastien OTTAVIANI for Bichat Hospital (Paris, APHP)
- Prof. Thomas BARDIN, Prof. Pascal RICHETTE, Prof. Frédéric LIOTE, Prof. Hang-Korng EA and Dr. Augustin LATOURTE for Lariboisière Hospital (Paris, APHP)

The first visit took place between January 1, 2016 and June 1, 2019, and was the index date. Data collection including follow-up visits, from computerized medical files, took place from January 1, 2016 to June 1, 2021.

3.2 Data collection

Some data on the study population were recorded only at M0, some ones were recorded at each visit, and some are globally recorded on the two years of follow up. For more details, we thank the learner to refer to the results of the first part of our study (URATE-CHALLENGE 1: Gout patients profile and management in referral centres: results of a real-world multicentric study; Materials and Methods, Part 2).

3.3 Outcome measures

In order to determine the predictors of target uricemia, we implemented bivariate mixed models, followed by a multivariate mixed model, explaining the reach of 360-

target at each visit (M6, M12, M24).

It was planned to implement logistic generalized mixed models incorporating the patient within the centre in random effects. However, the first analyses on a subgroup of explanatory variables showed a very weak random effect linked to the centre. Thus, the centre has been removed from the random effects, and only the patient appears as a random effect in the different estimated models.

3.4 Statistical Analysis

For the primary objective, we have first set up a bivariate generalized mixed model, to investigate the relationship between 360-target achievement at each visit (uricemia < 6.0mg/dL) and an explanatory variable of interest (fixed effect). Each model also contained the visit as a fixed effect to account the time effect, and the patient as a random effect to account the correlation between the data due to the repeated nature of the data.

Following this, we set up a multivariate generalized mixed model, using the explanatory variables that had a p-value < 0.2 in the bivariate analyses. We started with an initial model, integrating only the fixed effect visit, to which we applied an automatic bottom-up variable selection algorithm, based on AIC criteria, which allowed us to obtain the final model, the "complete" model. In case of convergence problems, the number of iterations allowed was increased.

For the subgroup analysis on the relationship between being at the 360-target and kidney function, we performed a Fisher exact test, due to the small effective.

For the ULT tolerance data, and the extra-rheumatologic effects, we performed a descriptive analysis of the data: means (standard deviation, SD) for continuous variable with normal distribution, medians (interquartile range, IQR) otherwise, minima and maxima were calculated for the quantitative variables, while numbers and frequencies were calculated for the qualitative variables.

We consider a significance level of 5% for all analyses. The statistical analyses were carried out with the R software (version 4.0.5), by the biostatistics unit of the GHICL Clinical Research and Innovation Delegation.

3.5 Patient informations and ethical considerations

This study is qualified as a research not involving the human person (RNIHP). The study protocol was submitted to the GHICL Internal Research Ethics Committee for review on 19 January 2021 (Project reference: RNIPH-2021-02).

Each patient included in the study received an information letter, specifying the nature of transmitted informations, the data recipients, the length of time the data would be kept, and a reminder of their rights. This information letter was sent by post, with acknowledgement of receipt, to included patients of the research, and accompanied by an objection form to be returned if the patient wished so.

In addition to this specific information, each patient was informed by the following sentence on their summons: "Your data may be used for medical research purposes. For further information, you can contact the Correspondant Informatique et Libertés Recherche at the following address: correspondant.recherche@ghicl.net ".

4 Results

The design of the mixed models means that the presence of missing data does not exclude a patient from the analysis: a patient with no uricemia value (explained variable) at M6, for example, but with values at M12 and M24, can be taken into account. However, a patient must have at least one uricemia value at M6, M12 or M24 to be included in the analysis.

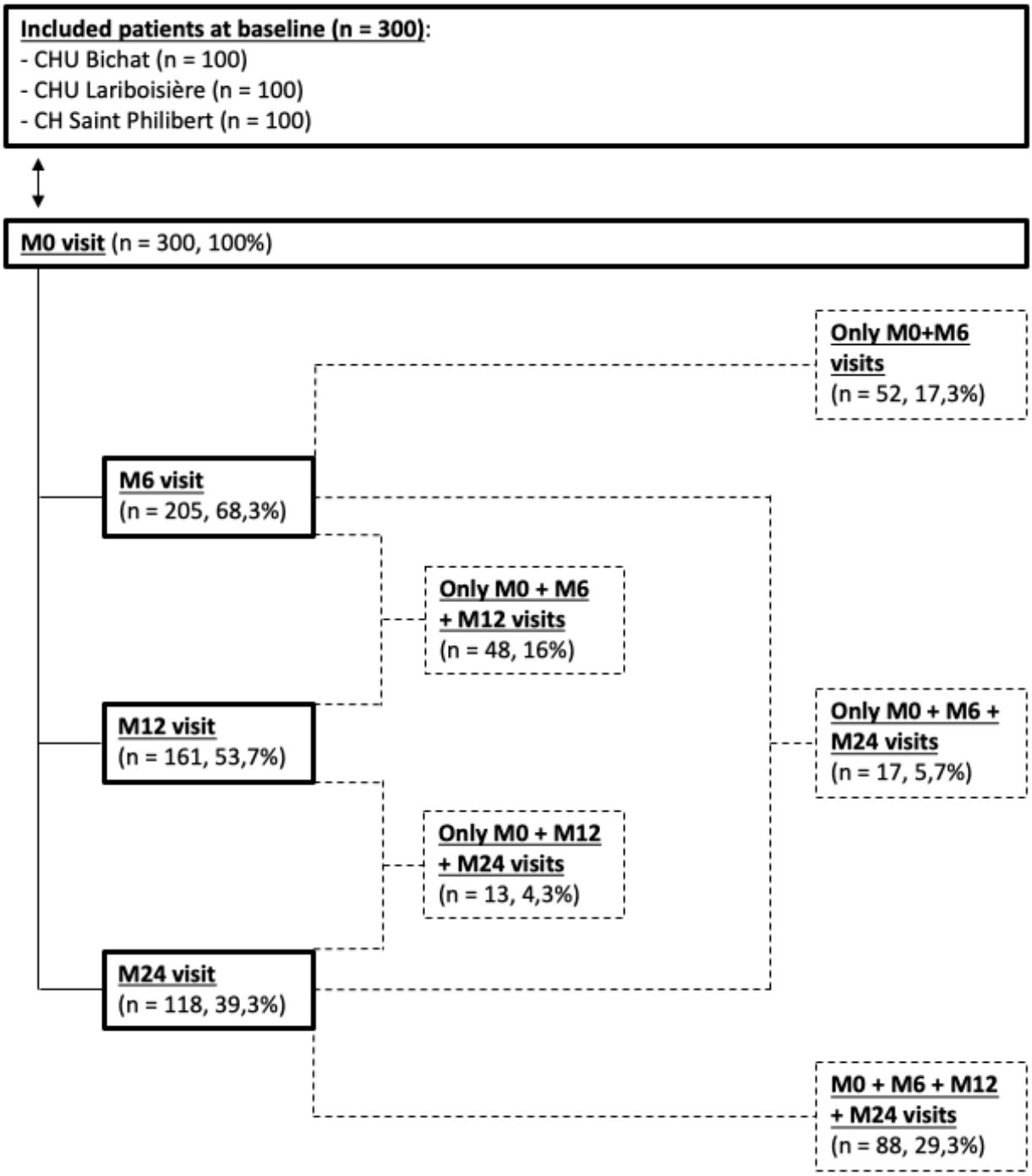
Of the 300 patients included in the study, 66 (22%) only visited at M0. These are therefore excluded from the analysis. Of the 234 patients who completed at least one other visit, 25 had no SU values at either M6, M12 or M24. These patients are therefore also excluded from the following analysis.

Thus, the research of predictive factors for reaching the 360-target was carried out on a sample of 209 patients and a total of 405 observations (patient x visit). Of these 209 patients, 70 (33.5%) had a single follow-up visit, 82 patients (39.2%) had two visits, and 57 patients (27.3%) had three visits.

4.1 Flowchart

Patients didn't all completed the four visits, but the absence to one visit didn't necessarily imply the absence to the future visits (for example, if an absence was justified by an intercurrent health problem). Thus, a patient who only visits at M0 and M6, for example, will be listed as a lost to follow-up at M12 and at M24, as the reason for not visiting may change between each visit (**Figure 4**).

Figure 4. Study flow chart



A total of 300 patients were included in the study between January 1, 2016 and June 1, 2019: 100 patients in each tertiary care center. Study population characteristics are presented in **Tab.12**. For more details, we thank the learner to refer to the results of the first part of our study (URATE-CHALLENGE 1: Gout patients profile and management in referral centres: results of a real-world multicentric study, Results, Part 1, **Tab.1**).

Table 12. Baseline Population

Parameters	*Effective (%)*	*Mean ± SD*	*Median [Q1-Q3]*	*Min - Max*	*Missing data (n)*
Center					
• CHU Bichat	100 (33.3%)	-	-	-	0
• CHU Lariboisière	100 (33.3%)	-	-	-	0
• CH Saint-Philibert	100 (33.3%)	-	-	-	0
Humankind					0
• Women	57 (19%)	-	-	-	
• Men	243 (81%)	-	-	-	
Age at inclusion (years)	-	62.2 ± 15.2	64 [53; 74]	17 - 97	0
Ethnicity					9
• Caucasian	163 (56%)	-	-	-	
• North Africa	49 (16.8%)	-	-	-	
• Sub Saharan Africa	48 (16.5%)	-	-	-	
• South East Asia	15 (5.2%)	-	-	-	
• Middle East	2 (0,7%)	-	-	-	
• Others	14 (4.8%)	-	-	-	
BMI (kg/m^2)	-	27.9 ± 4.9	27.2 [24.8; 30.4]	13.5 - 49	53
Diet rich in purine and/or fructose	116 (47%)	-	-	-	53
Practice of regular physical exercise	31 (12.6%)	-	-	-	53
Socio-economic status					38
• Managers	14 (5.3%)	-	-	-	
• Academic profession	39 (14.9%)	-	-	-	
• Workers, farmers	35 (13.4%)	-	-	-	
• Unemployed	13 (5%)	-	-	-	
• Home keeper, or retired, or disabled	161 (61.5%)	-	-	-	
Smocking status					1
• No-smoker	190 (63.5%)	-	-	-	
• Current smoker	41 (13.7%)	-	-	-	
• Former smoker	68 (22.7%)	-	-	-	
Beverages (alcohol and/or soda)					1
• No	194 (64.9%)	-	-	-	
• Current	75 (25%)	-	-	-	
• Former	30 (10%)	-	-	-	
Hyperuricemic treatment, in patient's medical order					1
• 0	103 (34.4%)	-	-	-	
• 1	70 (23.4%)	-	-	-	
• ≥ 2	126 (42.1%)	-	-	-	
Hypouricemic treatment, in patient's medical order					1
• 0	126 (42.1%)	-	-	-	
• 1	95 (31.8%)	-	-	-	
• ≥ 2	78 (26.1%)	-	-	-	
If yes, presence of a terminal kidney failure treatment (dialysis, kidney transplant)	4 (1.3%)	-	-	-	
Personal history of other rheumatological disorders	**100 (33.4%)**				1
• Osteoarthritis	72 (72%)	-	-	-	
• Hydroxyapatite crystal disease	22 (22%)	-	-	-	
• Primary hyperparathyroidism	2 (2%)	-	-	-	
• Rheumatoid arthritis	2 (2%)	-	-	-	
• Psoriasic arthritis	4 (4%)	-	-	-	
• Others	13 (13%)	-	-	-	
of which, patients with ≥ 2 comorbidities	17 (17%)	-	-	-	
Personal gout complication at inclusion	225 (75%)	-	-	-	0
• Tophus*	144 (48%)	-	-	-	
• Renal lithiasis on imaging and or renal colic	35 (11.7%)	-	-	-	
• Chronic renal failure	128 (42.7%)	-	-	-	
• Gouty arthropathy	58 (19.3%)	-	-	-	

Personal history of other comorbidities					
• Diabetes mellitus	**84 (28.1%)**	-	-	-	1
Type 1	2 (2.4%)	-	-	-	
Type 2: non-insulin-dependent	56 (66.7%)	-	-	-	
Type 2: insulin-dependent	26 (31%)	-	-	-	
• Arterial hypertension	**181 (60.5%)**	-	-	-	1
• Cardiovascular history	**76 (25.4%)**	-	-	-	1
Cerebral stroke	17 (22.4%)	-	-	-	
Acute PAOD and/or coronaropathy	42 (55.3%)	-	-	-	
VTE	9 (11.8%)	-	-	-	
• Congestive heart failure	**38 (12.7%)**	-	-	-	1
• Dyslipidemia	**100 (33.4%)**	-	-	-	1
• Liver disease	**11 (3.7%)**	-	-	-	1
• Obesity (ie BMI > 30 kg/m^2)	**74 (24.6%)**				53
Family history of					
• Gout	**55 (18.3%)**	-	-	-	0
First degree	46 (83.6%)	-	-	-	0
Second degree	9 (16.4%)	-	-	-	0
• Renal colic	**5 (1.7%)**	-	-	-	0
• Hyperuricemia	**2 (0.7%)**	-	-	-	0
Age at diagnostic (years)	-	56 ± 17.3	58 [45; 68]	15 - 94	13
Duration of the disease before inclusion (years)	-	5.8 ± 8.6	2 [0.2; 8]	0 - 53	14
Number of gout flares over the last 6 months	-	2.1 ± 2.8	1 [1; 2]	0 - 20	18
Joint distribution at inclusion					1
• mono-articular	93 (31.1%)	-	-	-	
• oligo or poly-articular	206 (68.9%)	-	-	-	
Initial uricemia, at inclusion (mg/dL)					17
• Global	-	8.18 ± 2.37	8.15 [6.7; 9.5]	1.7 - 16.5	
• In naïve for ULT patients	-	7.25 ± 2.33	7.35 [5.5; 8.72]		
• Non-naïve for ULT patients	-	8.78 ± 2.21	8.61 [7.48; 9.9]		
Naïve for ULT					0
• No**	117 (39%)	-	-	-	
• Yes	183 (61%)	-	-	-	
If current urate lowering therapy at inclusion					0
• Allopurinol (*effective*), and posology (*mean, median, min-max*)	45 (55.6%)	173.3 ± 84.3	150 [100; 200]	50 - 300	
• Febuxostat (*effective*), and posology (*mean, median, min-max*)	34 (42%)	84.7 ± 19.1	80 [80; 80]	40 - 120	
• Benzobromarone, Probenicide	2 (2.4%)	-	-	-	
• Lesinurad	0 (0%)	-	-	-	
• Rasburicase, Pegloticase	0 (0%)	-	-	-	
• Bithérapie	0 (0%)	-	-	-	
First consultation context					0
• Consultation	190 (63.3%)	-	-	-	
• Hospitalization	110 (36.7%)	-	-	-	
If specifically referred in expert centre, reason	**178 (59.3%)**	-	-	-	0
• from primary care, for treatment initiation	9 (5.1%)	-	-	-	
• from another hospital department for gout management	140 (78.7%)	-	-	-	
• non-control at a submaximal dose of ULT***	9 (5,1%)	-	-	-	
• non-control at a maximal dose of ULT***	5 (2.8%)				
• non-control with non-referred management	1 (0.6%)	-	-	-	
• for initial hospital prescription	1 (0.6%)	-	-	-	
• already follow in the expert center for another rheumatological pathology	9 (5.1%)	-	-	-	
• from primary centre, for re-evaluation	2 (1.1%)	-	-	-	
• for personal convenience	2 (1.1%)	-	-	-	

** clinical or ultrasound tophus*
*** anterior or actual, introduce before M0*
**** in primary care*

4.2 Results of the bivariate mixed models, and of the complete mixed model (n = 405), explaining the reach of the 360-target

These logistic generalized mixed models, explaining goal attainment at each visit, incorporating the patient as a random effect, and two explanatory variables (fixed effects) at each visit: a predictive factor of interest (first column of the table below), and the visit (M6/M12/M24).

Groupings were made for some variables composed of too many modalities (insufficient classes): this concerns ethnicity and beverage consumption.

Some variables have a very wide confidence interval around the odds ratio, but are presented in the table below for completeness. Despite this, some variables could not be included in the bivariate analysis: dialysis at inclusion (the only patient with dialysis at inclusion only completed the visit at M0), transplant during follow-up (the only patient with a transplant had it between M12 and M24, and has no uricemia value at M24), Probenecid intake during follow-up (the only patient who took Probenecid during his follow-up had it on arrival at the M6 consultation and has no uricemia value at this visit), ALLO 401-500mg/day taken during follow-up (all patients who took this dose achieved the 360-target, n = 4 patients), FBX >120mg/d during follow-up (all patients taking this dose achieved the 360-target, n = 2 patients).

In the bivariate mixed models, we notice a statistical significance of age at gout onset and age at follow-up starting (p-values = 0.007 and 0.011 respectively): increasing these variables by one unit (i.e. one year) increases the probability of reaching the 360-target by 1.03 (OR = 1.03, CI95% = [1.01-1.06] for both variables). Thus, the probability to reach the 360-target as age increases by one year, is 3%. The presence of a tophus on joint ultrasound increased the probability to reach the 360-target by 2.63 (OR = 2.63, CI95% = [1.20; 5.74]) (**Table 13**).

Compliance with ULT when arriving to the consultation multiplies by 35.36 the probability to reach the 360-target at this visit (OR = 35.36, CI95% = [5.46; 229.08]). The confidence interval is very wide, therefore very imprecise, due to the low proportion of non-compliance among patients with 360-target (6.4%) (**Table 13**).

For categorical variables with more than 2 modalities (beverage consumption, ethnicity, ALLO dosage before consultation), we also conducted type 1 ANOVAs between the model containing the explanatory variable in question and the visit, and

the model containing only the visit as an explanatory variable. This allows us to obtain a single p-value for the variable, indicating its overall significance, rather than a p-value per modality, which does not allow us to conclude on the overall significance of the variable. Thus, there was no overall significance for the ethnicity and beverage consumption variables (p-values = 0.15 and 0.76 respectively), but overall significance for the ALLO variable (p-value = 0.0006) (**Table 13**).

Those following parameters were not reported in Tab. 13, because of no-significance : gout duration at inclusion, being naïve or not of hypouricemic treatment, beverage consumption at inclusion, having rheumatological comorbidities (including osteoarthritis), the time between the onset of gout and the start of follow-up in an expert centre, ethnicity, BMI, the presence of hyper or hypouricemic treatment in the patient's background treatments, the presence of extra-rheumatological comorbidities as collected in **Tab. 12**.

Then we set up a multivariate mixed model, based on the list of variables with a p-value < 0.2 in the bivariate analysis: tophus on articular ultrasonography, age at gout setup, age at follow-up starting, ethnicity, THU observance, removal of a hyperuricemic therapy from the patient's background treatment, ALLO dosage before consultation.

We carried out an automatic, bottom-up, selection of variables, based on the "Akaike" criterion (AIC). The AIC is a versatile indicator, assessing the good fit of a model, and allowing to compare several models with each other.

We started with the model that integrates only the visit as an explanatory variable (in order to always take into account the effect of time), and then we added one by one each of the variables in the above list. At each stage, the model retained is the one that minimises the AIC. When the addition of explanatory variables leads only to models with an AIC higher than the one of the current model, the algorithm stops: we obtain the "complete" model. In our case, some models failed to converge. If increasing the number of iterations had not solved the problem, we would have removed the offending explanatory variable from the selection.

The complete-model, after variable selection, contains 4 explanatory variables (fixed effects), in addition to the visit (**Table 14**); similarly to the bivariate analysis, we do not display the visit variable because its interpretation is not relevant to our analysis.

The presence of tophus on joint ultrasound increased the likelihood of reaching the 360-target by 3.07 (OR = 3.07, CI95% = [1.08; 8.69]) (**Table 14**). A one-unit (one-year) increase in age, increased the probability of reaching the 360-target by 1.05 times (OR = 1.05, CI95% = [1.01; 1.09]). This translates into a 5% increase in probability (**Table 14**). ALLO prescription at a dosage ≤200mg/d didn't significantly increase the probability of achieving the 360-target, compared with no ULT prescription (p-value = 0.79), but there was a significant increase in the odds for >200mg/d prescriptions before the visit to assess achievement: the odds increased by 6.57 for these patients (OR = 6.57, CI95% = [1.58; 27.3]). However, the CI95% and the standard error are high, due to the small number of patients with this dosage who didn't reach the 360-target. This result should therefore be interpreted with caution due to its imprecision and should be confirmed on a larger sample size (**Table 14**).

We notice that compliance is not present in the final model, despite its high significance in the bivariate analysis. Initially, the variable was retained by the algorithm, but due to the unevenness of the distribution, it distorted the model with a very high 95% CI around the OR and standard error. This is due to the small number of non-compiling patients included in the statistics, as probably most of the non-compiling patients are the one losses to follow-up. It was therefore removed from the analysis. This suggests, however, that compliance is also an important predictor of achieving the 360-target, which seems natural (**Table 14**).

Table 13. Bivariate and complete mixed model: predictive factors of 360-target

		Bivariate mixed models: predictive factors of 360-target			**Complete mixed model: predictive factors of 360-target (n = 405, AIC : 268.8)**
		360-target achieved	*360-target not achieved*	*Odds-Ratio (OR) (IC95%, p-value)*	*Odds-Ratio (OR) (IC95%, p-value)*
Gout duration before inclusion (y)	Mean ± SD	5.8 (8.0)	5.6 (7.5)	0.996 (0.95-1.04, p=0.866)	-
Naïve status for THU at inclusion	No	54 (37.2)	91 (62.8)	-	-
	Yes	80 (30.8)	180 (69.2)	1.38 (0.69-2.77, p=0.360)	-
Beverage consumption at inclusion	No	82 (33.3)	164 (66.7)	-	-
	Yes	13 (34.2)	25 (65.8)	0.69 (0.21-2.29, p=0.545)	-
Ethnicity	Caucasus	71 (29.8)	167 (70.2)	-	-
	North Africa	23 (32.9)	47 (67.1)	0.81 (0.31-2.12, p=0.663)	-
	Sub Saharan Africa	20 (42.6)	27 (57.4)	0.38 (0.12-1.15, p=0.087)	-
	Others	18 (45.0)	22 (55.0)	0.36 (0.11-1.17, p=0.089)	-
BMI (kg/m^2)	Mean ± SD	28.2 (5.5)	28.3 (4.8)	0.995 (0.93-1.07, p=0.892)	-
Hypertension	No	56 (36.6)	97 (63.4)	-	-
	Yes	76 (30.4)	174 (69.6)	1.47 (0.74-2.95, p=0.273)	-

Major cardiac event	No	98 (33.3)	196 (66.7)	-	-
	Yes	34 (31.2)	75 (68.8)	0.99 (0.46-2.12, p=0.976)	-
Diabetes Mellitus	No	97 (33.4)	193 (66.6)	-	-
	Yes	35 (31.0)	78 (69.0)	1.24 (0.58-2.64, p=0.577)	-
Congestive heart failure	No	117 (32.1)	247 (67.9)	-	-
	Yes	15 (38.5)	24 (61.5)	0.77 (0.26-2.32, p=0.648)	-
Dyslipidemia	No	90 (33.6)	178 (66.4)	-	-
	Yes	42 (31.1)	93 (68.9)	1.13 (0.55-2.31, p=0.736)	-
Hepathopathy	No	124 (32.1)	262 (67.9)	-	-
	Yes	8 (47.1)	9 (52.9)	0.39 (0.07-2.05, p=0.264)	-
Number of complications at M0	Mean ± SD	1.3 (0.9)	1.4 (1.0)	1.09 (0.77-1.55, p=0.619)	-
Tophus identified with joint ultrasound	No	43 (39.4)	66 (60.6)	-	-
	Yes	34 (23.4)	111 (76.6)	2.63 (1.20-5.74, **p=0.015**)	3.07 (1.08-8.69, **p=0.035**)
Double contour sign identified with joint ultrasound	No	28 (26.7)	77 (73.3)	-	-
	Yes	49 (32.9)	100 (67.1)	0.68 (0.32-1.48, p=0.334)	-
DECT UMS deposits at inclusion	No	10 (22.7)	34 (77.3)	-	-
	Yes	27 (23.7)	87 (76.3)	0.73 (0.22-2.43, p=0.603)	-
Age at gout onset (years)	Mean ± SD	52.1 (17.0)	57.3 (16.2)	1.03 (1.01-1.06, **p=0.007**)	1.05 (1.01-1.09, **p=0.015**)
Age at follow-up starting (years)	Mean ± SD	59.0 (16.4)	63.2 (14.7)	1.03 (1.01-1.06, **p=0.011**)	-
THU observance before consultation	No	41 (70.7)	17 (29.3)	-	-
	Yes	72 (22.4)	249 (77.6)	35.36 (5.46-229.08, **p=0.0002**)	-
Allopurinol prescription before consultation	No	72 (33.0)	146 (67.0)	-	-
	Yes, ≤200mg/j	42 (48.8)	44 (51.2)	0.48 (0.22-1.07, p=0.073)	1.16 (0.39-3.46 ; p = 0.79)
	Yes, >200mg/j	20 (19.8)	81 (80.2)	3.01 (1.21-7.47, p=**0.018**)	6.57 (1.58-27.3 ; **p=0.01**)
Febuxostat prescription ≤80mg/j before consultation	No	70 (31.8)	150 (68.2)	-	-
	Yes	43 (26.7)	118 (73.3)	1.53 (0.68-3.44, p=0.300)	-
Febuxostat prescription 81-120mg/j before consultation	No	109 (30.3)	251 (69.7)	-	-
	Yes	4 (19.0)	17 (81.0)	2.14 (0.34-13.51, p=0.420)	-
Add of a hyperuricemic therapy from the patient's background treatment	No	126 (33.2)	253 (66.8)	-	-
	Yes	8 (30.8)	18 (69.2)	0.78 (0.24-2.58, p=0.690)	-
Removal of a hyperuricemic therapy from the patient's background treatment	No	122 (32.1)	258 (67.9)	-	-
	Yes	11 (50.0)	11 (50.0)	0.29 (0.07-1.10, p=0.069)	0.36 (0.06-2.10; p=0.25)
THU switch at consultation	No	65 (28.3)	165 (71.7)	-	-
	Yes	6 (33.3)	12 (66.7)	0.83 (0.17-4.02, p=0.820)	-
concordance of THU prescription with French recommendations	No	3 (37.5)	5 (62.5)	-	-
	Yes	105 (30.5)	239 (69.5)	1.08 (0.11-10.36, p=0.948)	-

4.3 Prediction of goal attainment according to the THU used: comparison of Allopurinol with Febuxostat

The proportion of patients completing all visits was slightly higher in patients with ALLO (**Table 14a**). The proportion of patients achieving M6 visit was similar in both groups, but it was noticed that follow-up over time seemed to be better for patients with ALLO vs. FBX (**Table 14b**). The reasons for discontinuation of follow-up may vary between patients, and are not just "true" losses of follow-up ones. Achievement of the 360-target is more frequent at M6 among patients on FBX, but the proportions are closer at M12 and M24, and the trend is reversed (**Table 14b**).

Table 14a. Achieved visits according to THU at M0 discharge among patients who did not change treatment during follow-up (n = 215)

	Allopurinol	*Febuxostat*
n	98	117
M0 only	24 (24.5%)	32 (27.4%)
M0+M6	18 (18.4%)	27 (23.1%)
M0+M12	4 (4.1%)	4 (3.4%)
M0+M24	2 (2%)	0 (0%)
M0+M6+M12	12 (12.2%)	21 (17.9%)
M0+M6+M24	4 (4.1%)	5 (4.3%)
M0+M12+M24	4 (4.1%)	3 (2.6%)
M0+M6+M12+M24	30 (30.6%)	25 (21.4%)

Table 14b. Visits made and goal achievement, according to THU at M0 discharge, among patients who did not change of treatment during follow-up (n = 215).

		Missing data	*Allopurinol*	*Febuxostat*
	n	/	98	117
M6	Achieved visit	/	64 (65.3%)	78 (66.7%)
	Achieved 360-target	25	32 (57.1%)	43 (70.5%)
M12	Achieved visit	/	50 (51%)	53 (45.3%)
	Achieved 360-target	12	31 (72.1%)	33 (68.8%)
M24	Achieved visit	/	40 (40.8%)	33 (28.2%)
	Achieved 360-target	15	26 (83.9%)	21 (77.8%)

4.4 Data from the global follow-up: extra-rheumatologic events

Only 6 patients (2%) developed a comorbidity during the two years of follow-up, mostly diabetes with 3 patients (50%), and only 5 patients (1.7%) developed a major cardiovascular event (**Table 15**).

101 of the 300 included patients, completed the M12+M24 visits. Of these, 42 patients had an eGFR <90 mL/min at M12 and an eGFR value at M24. Of these 42 patients, one did not have a uricemia value at M12.

Thus, the analysis to compare the evolution of eGFR between M12 and M24 according to the 360-target achievement at M12, among patients with a GFR < 90 mL/min at M12, was done on 41 patients (**Table 16**). Among these 41 patients, there were 12 (29.3%) with a eGFR increase ≥ 5%, and 29 (70.7%) with a decrease or increase < 5%. We performed a Fisher exact test, due to the small numbers.

Among patients without goal attainment at M12, 2 patients (16.7%) showed an increase in eGFR; among patients with goal attainment at M12, 10 (34.5%) showed an increase in eGFR. There was no significant difference between the two groups (p-value = 0.45); this may be due to lack of power due to the small sample size (**Table 16**).

Table 15. Extra-rheumatologic events during the two years of follow-up (n = 300)

	Missing data (n)	Effective (%)
Comorbidity development during the two years of follow up • Yes • No If yes, type*: • Diabetes mellitus[1] • Arterial hypertension • Chronic kidney disease • Dyslipidemia[2] • PAOD[3] • Hepatopathy[4]	0	 6 (2%) 294 (98%) 3 (50%) 0 (0%) 0 (0%) 1 (16.7%) 1 (16.7%) 2 (33.3%)
Major cardiovascular event during the two years of follow up • Yes • No If yes, type*: • Cerebral stroke[5] • Acute PAOD and/or coronaropathy[6] • VTE	0	 5 (1.7%) 295 (98.3%) 2 (40%) 3 (60%) 0 (0%)

[1] : 1 patient with Febuxostat 40mg/d introduced at M0 and then lost to follow-up, 1 patient with Febuxostat 80mg/d introduced at M0 and continued throughout of the follow-up, and 1 patient with Allopurinol introduced at 100mg/d at M0 and continued throughout the follow-up up to 300mg/d.
[2] : 1 patient with Allopurinol introduced at 100mg/d at M0 and continued throughout the follow-up to 300mg/d.
[3] : 1 patient on Allopurinol 100mg/d already present at M0 and continued throughout the follow-up
[4] : 1 patient with Febuxostat 80mg/d introduced at M0 and continued throughout the follow-up, and 1 patient with Allopurinol introduced at M6 and continued throughout the follow-up to 400mg/d.
[5] : 2 patients on Febuxostat (doses between 40 and 80mg/d).
[6] : 1 patient with Febuxostat up to 120mg/d at M6, followed at M6 by allopurinol 200mg/d, 1 patient on Febuxostat 40mg/d at M0 then lost to follow-up, 1 patient on Febuxostat 40mg/d introduced at M0 and continued throughout the follow-up at 80mg/d.

Table 16. Comparison of eGFR evolution between M12 and M24 according to the achievement of the 360-target at M12 (n = 41)

		Missing data (n)	*360-target achieved at M12*	*360-target not achieved at M12*	*p-value*
n		/	12 (29.3%)	29 (70.7%)	/
eGFR increase ≥ 5%	No	0	10 (83.3%)	19 (65.5%)	0.45
	yes		2 (16.7%)	10 (34.5%)	

4.5 Data from the global follow-up: Side effects of the most commonly gout treatments used, before inclusion and during the two years of follow-up

Concerning side effects during medical history and the two years of follow-up, it was principally non-severe allergic reaction for ALLO with 11 (3.7%) patients, digestive intolerance for FBX with 6 (2%) patients, and digestive intolerance for Colchicine with 56 (18.7%) patients (**Table 17**).

Table 17. Data from the global follow up (n = 300)

	Missing data (n)	Effective (%)
Over the two years of follow-up and in the patient's history, adverse events related to Allopurinol* • digestive • hepatic • non-severe allergic reaction • DRESS syndrome • thymic	0	 5 (1.7%) 1 (0.3%) 11 (3.7%) 2 (0.7%) 1 (0.3%)
Over the two years of follow-up and in the patient's history, adverse events related to Febuxostat* • digestive • renal • hepatic • skin rash • skin oedema • allergic reaction	0	 6 (2%) 1 (0.3%) 2 (0.7%) 3 (1%) 1 (0.3%) 2 (0.7%)
Over the two years of follow-up and in the patient's history, adverse events related to Colchicine* • digestive • neuromuscular • hematologic • renal • angioedema • hepatic	0	 56 (18.7%) 3 (1%) 1 (0.3%) 2 (0.7%) 4 (1.3%) 2 (0.7%)

Abbreviations: PAOD = Peripheral arterial occlusive disease;
* plusieurs possibles

4.6 Predictive factors of "lost to follow-up" patients: subgroup analysis to compare "lost to follow-up after M0" and "at least 2 consultations achieved" patients profile

A subgroup analysis was carried out to compare the group of patients that have been lost to follow-up just after M0, to the group of patients that have undergone at least 2 consultations (n = 300), in order to study the predictive factors of sight loss differentiating these 2 groups (**Table 18**). Two variables were statistically significant: there was a lower probability of sight loss in the follow-up if the context of the first meeting was a consultation, and if the disease was of longer duration.

Table 18. Subgroup analysis to compare "lost to follow-up after M0" and "at least 2 consultations achieved" patients profile (n = 300)

	Missing data (n)	*"lost to follow-up" after M0 (n = 66)*	*M0 and at least one another consultation (n = 234)*	*p-value*
ULT prescribed at the end of the M0 consultation (%) • Allopurinol • Febuxostat	0	57 (86.4%) 24 (42.9%) 32 (57.1%)	197 (84.2%) 102 (53.1%) 90 (46.9%)	0.81 0.23
M0 meeting context (%) • consultation • hospitalization	0	 32 (48.5%) 34 (51.5%)	 158 (67.5%) 90 (46.9%)	 **0.0072**
Age at inclusion (years) * *Mean ± SD* *Median [Q1-Q3]*	0	 63.6 ± 13.4 64 [57.2 ; 72.8]	 61.8 ± 15.7 64 [52 ; 74]	 0.61
Age at gout diagnosis (years) * *Mean ± SD* *Median [Q1-Q3]*	13	 59.7 ± 15.5 61 [51 ; 69]	 55 ± 17.6 57 [43 ; 68]	 0.056
Duration of disease before inclusion (y) *Mean ± SD* *Median [Q1-Q3]*	14	 4.2 ± 6.6 1 [0 ; 5]	 6.3 ± 9 3 [0.5 ; 8]	 **0.02**
Number of gout flares over the last 6 months before inclusion* *Mean ± SD* *Median [Q1-Q3]*	18	 1.9 ± 2.4 1 [1 ; 2]	 2.2 ± 2.8 1 [1 ; 2]	 0.39
M0 uricemia (mg/dL)** *Mean ± SD* *Median [Q1-Q3]*	17	 8.09 ± 2.54 7.92 [6.56 ; 9.45]	 8.21 ± 2.33 8.2 [6.8 ; 9.5]	 0.75
Gout complications before M0* (n) *Mean ± SD* *Median [Q1-Q3]*	0	 1 ± 0.8 1 [0 ; 2]	 1.2 ± 1 1 [1 ; 2]	 0.21
Extra-rheumatologic comorbidities (n) *Mean ± SD* *Median [Q1-Q3]*	1	 1.8 ± 1.5 2 [1 ; 2]	 1.6 ± 1.4 1 [0 ; 3]	 0.51

** Test de Mann-Whitney-Wilcoxon,*
*** Test de Student*

5 Discussion

5.1 Key results

5.1.1 Predictive factors for the 360-target achievement

There was a very small random effect related to the centre. This allowed to carry out the predictive factors analyses without taking centre into account. We can assume that this can be due to similar management by the rheumatologists in expert centres, similar characteristics of the initial populations.

In our study, age, gout duration and high crystal burden were both associated with better outcomes (**Table 13**), and the first meeting context of consultation and disease duration were associated with a higher likelihood that the patient will come to follow-up visits (**Table 18**). This suggests that it's never too late in life nor in the course of the disease to provide optimal management to a gout patient. This is an important finding, as the increase in the prevalence of gout seems to be partly explained by the population aging [3]. Indeed, in this population the proportion of patients with gout can be very high, up to 10% as shown in a recent Australian study of more than 11 000 institutionalized patients aged over 65 [68]. About the crystal charge, this allows us to hypothesize that patients with visible complications of the disease will take it more seriously and be compliant.

ALLO dosage > 200mg/d significantly increase by 6.57 the probability to reach the 360-target, whereas taking ALLO at a dosage of 200mg/d or less is equivalent to take nothing (**Table 13**). Even if the CI95% and the standard error are high, this point had already been described in other studies, and again underlines the importance of ALLO titration, often insufficiently performed in primary care [9]. Indeed, this is corroborated by French studies showing no significant change in the daily dosage of ALLO, and no change in the percentage of patients reaching the 360-target between 2008 and 2014, despite persisting high SU levels [49] [50]. More recently, a British study provided the same observation [26].

In the subgroup analysis comparing ALLO and FBX, neither of them seems to be more effective than the other when doses are optimized. According to **Tab. 14**, 360-

target achievement is more frequent at M6 among patients on FBX, but the proportions are closer at M12 and M24, and the trend is reversed, further supporting that SU targets are achieved more quickly (but also more abruptly) with FBX. Face-to-face studies, like the CONFIRMS trial [69], were unable to demonstrate superiority of ALLO or FBX, mainly because of incorrectly titration of ALLO : as lower number of "ALLO patients" achieved the objective, statistical analyses are non-contributive. However, these studies suggest that 300 mg/d of ALLO and 40 mg/d of FBX would have the same effect [69].

Although not included in the final model, adherence to THU is logically associated with the goal achievement: this predictive factor is expected and does not provide any new knowledge, but reaffirms the effectiveness of ULTs (**Table 13**).

Only one other study has been published in New Zealand in 2020, whose aims were to determine factors that predict SU lowering response to ALLO, and to determine a minimum therapeutic oxypurinol concentration (ALLO active metabolite) [70]. The minimum therapeutic oxypurinol concentration was found to increase with decreasing renal function. Although there is a positive relationship between change in oxypurinol and change in serum urate concentration, a minimum therapeutic oxypurinol is dependent on eGFR and cannot reliably predict serum urate target.

5.1.2 Side effects of the most commonly gout treatments used, before inclusion and during the two years of follow-up

We have recorded THU adverse events before inclusion and during the two years of follow-up, without distinction between these 2 periods due to the weak proportion of patients (**Table 17**).

The safety profile of these two treatments has already been evaluated in numerous studies [27,71,72]. The most frequent side effects of XOI in our study correspond to those already described.

Concerning ALLO, the side effects were mainly allergic and digestive, and for

FBX mainly digestive and hepatic. Concerning serious adverse events in our cohort, there were 2 patients with a history of DRESS syndrome: for these 2 patients, the episode had occurred before inclusion, and they were referred to an expert centre for therapeutic re-evaluation following this (**Table 17**). The first patient who has presented a DRESS syndrome to ALLO, was not living in France all the year: given the allergic risks and the need to monitor the introduction, ULT was initiated with delay. The patient was treated with FBX, and then, regarding a still very high uricemia, he was finally treated with Benzobromarone, allowing the objective to be achieved. The second patient who presented a DRESS syndrome to ALLO, was treated in the expert centre with a dual therapy of Benzobromarone and Rasburicase, as she also had presented an allergic skin reaction to FBX, but she was rapidly lost to follow-up.

Concerning FBX, the side effects were mainly digestive, and no cardiac side effect directly related to FBX introduction was noticed (**Table 17**). Regarding the literature, the CARES study showed a higher cardiovascular mortality with FBX compared to ALLO, i.e. suggesting to avoid FBX in patients with a severe cardiovascular history [67]. However, the CONFIRMS trial was intended to be reassuring on cardiovascular side effects, and that is corroborate with the recent FAST study at higher FBX doses than the CONFIRMS study : in these 2 studies, as in ours, there were no more cardiovascular events under FBX even in patients with a severe cardiovascular history [72]. These results should be interpreted with caution, as 45,0% of participants discontinued follow-up in CARES study and only 6,2% in the FBX group in FAST study. A recent South Korean retrospective cohort study on persistence rates between allopurinol and febuxostat as first-line, on 602 patients, shows that at 8-years of follow-up, 282 (46.8%) patients stopped taking XOIs: the most common reason for XOI withdrawal was poor health literacy (61.3%), and that ALLO had worse persistence rates than FBX among patients with gout [73].

Despite the generic marketing since 2017, FBX is less cost-effective than ALLO, and did not show superiority. The differences observed on cardiovascular mortality are probably to be understood as ALLO is probably more protective against cardiovascular mortality than FBX, rather than an increase in risk. Thus, the arguments are divergent regarding ALLO and FBX : French recommendations recommend FBX as a second-line treatment, particularly in cases of renal insufficiency [29].

Regarding to the symptomatic treatments, the side effects noted for colchicine

were mainly digestive, at an average dosage of 1mg/d (**Table 17**). The average dosage of 0.5 mg/d as found in the first part of our study (URATE-CHALLENGE 1) therefore avoids this digestive intolerance and is in line with current recommendations. However, this leaves little therapeutic margin before the onset of side effects, in a significant proportion of patients.

5.1.3 Extra-rheumatologic effects of the THU: the non-rheumatologic benefits

We have studied the comorbidity development and the occurrence of major cardiovascular events during the two years of follow-up, in the context of the metabolic syndrome spectrum (**Table 15**).

The diagnosis of a comorbidity occurred 6 times, essentially diabetes, under both treatments. Major cardiovascular events occurred 5 times, essentially in patients with FBX (**Table 15**). Due to the small number of patients in our cohort, any analysis was carried out on these patients concerning the correlation between the occurrence of these events, the treatment under which those events occurred, and the uricemia level when the event occurred. Pérez-Ruiz et al suggests that achieving a 360-target, necessary for the dissolution of MSU crystals, appears to be a protective factor against the occurrence of cardiovascular events [30].

Almost all patients received colchicine as recommended during their follow-up [29]. Our study was not designed for that, but as it was pointed out in the 2020 SFR recommendations, numerous studies had shown the beneficial impact of colchicine on improving cardiovascular risk, even at very low doses (0.5mg/d or 1mg/d) [74-76].

In a subgroup study, the objective was to see if being on 360-target at M12 resulted in improved renal function 1 year later. No improvement in renal function has been shown when patients are at 360-target, probably explained by the small number of patient due to the lack of renal function data available at M12 (**Table 16**). The association of hyperuricemia and kidney function is actually discussed in the literature, with contradictory conclusions. In a recent meta-analysis, hyperuricemia was associated with a significant risk of rapid decline in eGFR $\geqslant$3 ml/min/1.73m^2 per year

(OR 1.38, 95% CI 1.20-1.59; low certainty) [77], but the fact that being at 360-target improves renal function hasn't been proved.

5.1.4 Compliance with medical visits, and predictive factors in the lost to follow-up population

Concerning the difference between lost-to follow-up patients just after M0 vs. later in the follow-up, we can understand that, if first meeting is a hospitalization, the patient is probably very comorbid and it is difficult for them to attend all their follow-up appointments (**Table 18**). The fact that as long as the gout duration is, the less people are lost to follow-up mean that the lack of control of the disease and the occurrence of disease-related complications should make people more likely to pursue chronic disease monitoring. It is therefore probably necessary, in the ones with short-standing gout, to emphasize that ULT is a lifelong treatment and that if they stop it their management will start from scratch (**Table 18**).

5.2 Clinical and therapeutic implications, perspectives

The aim in future years is to do better than 80% of patients at the 360-target after a 2-years follow-up, taking into account in particular the founded predictive factors of 360-target.

Apart from the rapidly reach of 360-target after ULT initiation, there is a lack of studies on the long-term ULT persistence. Indeed, this persistence difficulty had already been reported in the 2015 GOSPEL study in primary care: the reasons for discontinuing ULT were difficulty in achieving uric acid levels below 6.0mg/dL (47%), lack of symptom relief (34%) or lack of compliance (23%) [55]. In the Alvarado-de la Barrera and al. study in 2019, which involved 500 patients, of whom 221 had severe gout (44%) and 279 had non-severe gout (56%) at baseline [78]. At five years' follow-up, 28% of patients were in remission, of the only 40 patients remaining in the study, and none of the severe gout patients achieved remission. It was concluded that 360-target and remission were difficult to achieve in patients with severe gout, the barriers being poor adherence to treatment, persistent tophi and loss to follow-up.

Two studies show that when people with gout receive full individualized education about gout, 100% want to receive ULT, and persistence is excellent (92%) at 1 year and remains high (91%) at 5 years [58,79].

It would be interesting to carry out a long-term study in expert centres in order to know the results of the current management of gout in expert centres on the long-term persistence of THU.

Two recent publications are related to this subject.

In the first one, the recent NOR-GOUT prospective study, the objective was to assess low-grade inflammation due to urate crystal deposits and their correlation with cardiovascular risk, by measuring carotid intima thickness and the presence of atheromatous plaques [80,81]. It shows that urate crystal deposits are associated with low-grade inflammation. As the crystals dissolution is very slow, patients need to continue the ULT as long as possible, as indeed after 2 years of well conducted treatment, the uratic stock is generally reduced but has not completely disappeared [82,83].

The second one, a recent Australian study, has worked on ULT maintaining and

stopping factors after gout recovery [84]. Motivations for discontinuing ULT included doubts about the necessity of long-term treatment, stopping side effects exposition, doubts about the side effects of prolonged treatment, lack of safety data on prolonged treatment, and the desire to use as little treatment as possible. Motivations to continue ULT were the absence of crisis, the acceptance of chronic treatment, the feeling of security with regular monitoring of uricemia and the absence of change desire. All these factors are very interesting for implementing a targeted therapeutic education and allowing a long term better management and a better maintenance of ULT.

A cardio renal assessment appears to be essential in a dedicated consultation, at the beginning of the management of gout. Studies with a longer-term follow-up of patients are needed to evaluate the impact of the currently proposed treatment on extra-rheumatologic comorbidities in particular. The interest of a controlled screening for cardiovascular co-morbidities is recalled by the fact that the prevalence of gout is increasing due to the increasing prevalence of these co-morbidities.

5.3 Strengths and limitations of the study

One of the strengths of our study is its multicentric character, allowing a study with a large number of different profiles. In addition, this study involved a cohort of 300 patients, that give power for statistical analysis. To our knowledge, this is one of the first study in the literature that investigate the predictive factors of reaching target uricemia.

This study has also several limitations. First, there is the inherent limitations of retrospective observational studies, with missing data and incomplete follow-up.

Secondly, follow-up period may be too short to assess all gout outcomes and particularly those related to CV and renal outcomes.

Third, concerning the impact of 360-target on the kidney, the "control" group of non-target patients is small thanks to the optimization of management in the reference centre, and that limits the power of comparisons.

Fourth, the collection of changes in background treatment and intercurrent events was only based on the patient's tertiary centre computerized file, so there may have been missing data.

6 Conclusion

Some factors have been identified to predict the achievement of the 360-target. First of all, the tophaceous character on joint ultrasound, probably mean that the visible signs of the disease are perceived by the patient as a factor of gravity and that they facilitate compliance. The age mean that it is never too late to refer a gout patient to a rheumatologist. The dosage of ALLO above 200mg/L underlines the interest of the T2T strategy in gout, as in other chronic diseases for which this strategy is already used. This strategy should be applied in primary care rheumatology settings to obtain the same results as in expert centres.

The role of 360-target is well known on the gout control, but the long-term impact on co-morbidities (notably cardiovascular and renal ones), is still poorly defined. Longer-term observational studies would provide data on the persistence of long-term THU, and perhaps highlight more significantly its benefits. Indeed, long-term studies attempts to evaluate the persistence of treatment have already been carried out, but for the moment with insufficient number of patients to extrapolate the data.

Standardized screening for comorbidities could be developed, for example via a systematic day-hospital at the beginning of the follow-up, as a part of the patient's therapeutic education strategy. Moreover, as some gout treatments such as colchicine have tight therapeutic margins, this is an additional argument for the implementation of systematic codified screening for gout comorbidities.

Finally, the number of patients lost to follow-up in our study highlights the persistent problem of compliance and prolonged follow-up of patients with gout, even in expert referral centers, hence the need for reinforced therapeutic education.

Discussion générale en français

Les recommandations françaises de 2020 représentent un intérêt majeur dans l'actualisation et la simplification des recommandations de prise en charge de la goutte. Leur application, nettement supérieure en centres experts qu'en soins primaires, permet une atteinte de l'objectif d'uricémie chez 80% des patients à 2 ans. Notre étude a reconfirmé que cette pathologie requiert de traitements simples chez la plupart des patients quelque-soit le nombre de comorbidités qu'ils présentent.

Une marge de progrès est donc encore possible, même en centre expert. Les hypothèses soulevées sont la mise en place d'une structuration de l'éducation thérapeutique par exemple via l'organisation systématique d'une hospitalisation de jour, un délai d'introduction plus court des traitements hypouricémiants, le renforcement du réseau ville-hôpital pour un suivi plus rapprochée des patients afin d'atteindre rapidement l'objectif d'uricémie. Notre étude montre toutefois que les centres experts ne font le plus souvent qu'appliquer une prise en charge conventionnelle simple et optimisée, parfaitement applicable en contexte non spécialisé. Une meilleure diffusion et application des recommandations 2020 de la SFR pourrait permettre aux centres experts de se focaliser sur les cas difficiles-à-traiter.

Par ailleurs, la prescription très prolongée de traitements symptomatiques des crises est le témoin d'une persistance prolongée de l'inflammation due aux microcristaux, et la proportion très importante d'effets secondaires de type digestif à la colchicine même à dose thérapeutique, appelle à rediscuter des indications des [IL1]i.

La place de l'imagerie de la goutte est définie sur le plan diagnostique, mais son intérêt dans le suivi est encore mal défini, bien que certaines équipes aient commencé à s'y intéresser.

Enfin, il existe actuellement un manque de données sur le maintien du THU à long terme. Ces données seraient utiles pour étudier l'impact d'une uricémie à l'objectif, sur les comorbidités cardio rénales notamment, à long terme.

Conclusion générale en français

Cette étude multicentrique rétrospective fournit des données sur le profil et la prise en charge de 300 patients dans trois centres français experts de la goutte. C'est la première étude de ce type, car des études similaires dans le passé se sont concentrées sur les soins de médecine générale.

Les patients pris en charge en centre expert présentent davantage de comorbidités notamment cardiovasculaires, mais ont dans l'ensemble les mêmes profils à baseline que les patients pris en charge en consultation de ville. Nos conclusions sur la prise en charge en centre expert, sont donc applicables aux résultats attendus de prise en charge en soins primaires, si les recommandations y étaient appliquées.

Les résultats de prise en charge en centre expert entre 2016 et 2019, montrent que les recommandations françaises de 2020 étaient déjà suivies avant leur publication. Leur application permet que la plupart des patients soient à l'objectif à 1 an et 2 ans de suivi, sous des thérapeutiques classiques. Nous concluons donc à une efficacité très satisfaisante de la prise en charge actuellement proposée par les recommandations françaises. Leur application insuffisante en soins primaires, où la plupart des patients goutteux sont suivis, et les difficultés d'observance, en soins primaires et en centre expert, renforce l'idée d'éducation thérapeutique à travers un réseau ville hôpital permettant notamment des consultations rapprochées. Un autre moyen d'amélioration de l'observance discutable serait une introduction plus précoce des ULT.

Les facteurs prédictifs d'atteinte de l'objectif d'uricémie sont multiples. Tout d'abord le caractère tophacé, signifie probablement que les signes visibles de la maladie sont perçus par le patient comme un facteur de gravité et qu'ils facilitent l'observance. L'âge signifie qu'il n'est jamais trop tard pour adresser un patient goutteux à un rhumatologue. La posologie d'ALLO supérieure à 200mg/L souligne l'intérêt de la stratégie du T2T dans la goutte, à l'image d'autres pathologies chroniques pour lesquels cette stratégie est déjà employée.

L'utilisation d'[IL1]i en centre expert n'est pas rare, mais les recommandations sont souvent dépassées sur le plan des indications retenues, du fait de leur caractère

très restrictif. D'autre part la molécule la plus prescrite est celle n'ayant pourtant pas l'AMM. Des recommandations plus claires dans ce domaine sont nécessaires.

Une standardisation du dépistage des comorbidités pourrait être développée, par exemple via un hôpital de jour systématique en début de prise en charge, s'intégrant dans la stratégie d'éducation thérapeutique du patient.

L'impact d'être à l'objectif est bien connu sur le contrôle de la goutte, mais l'impact à long terme sur les comorbidités notamment cardio-vasculaires et rénales est encore mal défini. Des études observationnelles plus prolongées permettraient d'avoir des données sur la persistance du traitement hypouricémiant au long cours, et peut-être de mettre en évidence de manière plus significative les bénéfices du contrôle de l'uricémie sur les comorbidités cardiovasculaires.

Enfin concernant l'utilisation d'imagerie de la goutte, le scanner double énergie reste l'imagerie la plus performante pour la quantification de la charge uratique, malgré des faux négatifs et faux positifs. Sa place dans la définition d'un objectif personnalisé d'uricémie et dans le suivi sont à discuter.

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Résumé :

Contexte : De récentes études ont montré un défaut d'application des recommandations sur la goutte en soins primaires, motivant la publication par la Société Française de Rhumatologie (SFR) de ses premières recommandations en 2020 (RECO). L'objectif principal de notre étude était d'évaluer les résultats de la prise en charge en centres experts, sur le contrôle de l'uricémie et la prévention des crises. Les objectifs secondaires étaient, de déterminer le profil des patients suivis, les facteurs associés à l'atteinte de l'objectif d'uricémie (<360µmol/L), et la concordance de prise en charge avec ces RECO.

Matériel et Méthodes : Notre population d'étude comportait 300 patients goutteux, inclus aléatoirement à partir des listes de consultation de rhumatologues de 3 centres experts français, et évalués à l'inclusion (M0, compris entre 2016 et 2019), puis à 6 mois (M6), à 1 an (M12) et à 2 ans (M24). Nous avons décrit le profil des patients et leur prise en charge, et mis en œuvre des modèles mixtes logistiques afin de déterminer les facteurs prédictifs d'atteinte de l'objectif d'uricémie.

Résultats : Le profil de notre population (81% d'hommes, âge moyen 62,2 ± 15,2 ans) était globalement similaire à celui des patients suivis en soins primaires. A M0, les RECO étaient déjà respectées pour 94,9% d'entre eux. Parmi les non perdus de vue, 59,4% étaient à l'objectif d'uricémie à M6, 67,9% à M12, et 78,6% à M24 ; 13,1% des patients faisaient encore des crises de goutte à M24. 3 principaux facteurs prédictifs de l'atteinte de l'objectif étaient retrouvés en analyse multivariée : la présence de tophus à l'échographie articulaire (OR = 3,07 [1,08 ; 8,69]), l'âge (augmentation d'un an) (OR = 1,05 [1,01 ; 1,09]), la prescription d'ALLO à une posologie > 200mg/j vs. aucune prescription (OR = 6,57 [1,58 ; 27,3]).

Conclusion : L'application des RECO était nettement supérieure en centre expert par rapport à ce qui est habituellement rapporté en soins primaires, notamment en France, et montre des résultats très satisfaisants. Les centres experts ne font le plus souvent qu'appliquer une prise en charge conventionnelle simple et optimisée. Une meilleure diffusion et application de ces RECO en contexte non spécialisé, en évitant l'inertie thérapeutique, pourrait permettre aux centres experts de se focaliser sur les cas difficiles-à-traiter.

Composition du Jury :

Président Monsieur le Professeur Bernard CORTET

Assesseurs : Monsieur le Professeur Pascal RICHETTE
Monsieur le Docteur Sébastien OTTAVIANI

Directeur de thèse : Monsieur le Professeur Tristan PASCART