Livret GEM N° 3

Décembre 2016

Mot du GEM

Chers amis

Notre Groupe d'Etudes Multicentriques (GEM) Resopso a été créé en Mai 2011 pour conduire des études rétrospectives et prospectives multicentriques à forte puissance sur le psoriasis.

L'objectif était de répondre à des questions pratiques concernant aussi bien les aspects épidémiologiques, cliniques et thérapeutiques posés par cette maladie, que son évolution dans le temps, ses comorbidités associées, l'environnement des patients et les difficultés rencontrées dans leur parcours de soin. En connaissant mieux la maladie et les problèmes qu'elle pose, nous pouvons ainsi grâce au GEM améliorer la prise en charge de nos patients souffrant de psoriasis.

Nous avons voulu aussi que chacun d'entre nous s'il le souhaite, qu'il soit libéral ou hospitalier, puisse monter, conduire et publier une étude d'intérêt sur le psoriasis, dans l'esprit convivial et d'entre aide de Resopso. C'est la raison d'être de notre GEM3.

Un vrai défi que nous avons su relever tous ensemble ! Comme en attestent les nombreuses publications et communications du GEM Resopso depuis 5 ans.

Aussi je tiens à remercier au nom de tous Emmanuel Mahé, à qui nous devons beaucoup et qui a accepté en 2015 de piloter notre groupe et son GEM3 et de coordonner notre activité scientifique au sein de Resopso. Grâce à lui nous avons pu mener à bien un grand nombre d'études. Nous avons pu les publier dans plusieurs revues internationales dont le prestigieux British Journal of Dermatology, et communiquer dans de grands congrès comme l'EADV.

Grâce à Emmanuel et à l'équipe GEM3, chacun d'entre nous peut mener à bien un projet d'étude sur un sujet d'intérêt pour nos patients psoriasiques. C'est le cas de Vitibio (psoriasis et vitiligo), publié récemment dans le JEADV (encore bravo à Laure Méry!).

Enfin et surtout, un très grand merci à tous pour votre participation enthousiaste et active à nos études, dans un esprit toujours aussi sympa et convivial. Vous faites vivre ainsi et se développer notre Groupe d'Etudes Multicentriques. Grâce à vous l'aventure continue, au profit des patients.

Nous vous donnons rendez-vous le jeudi 08 décembre pour notre soirée GEM à l'occasion des JDP. Cette soirée est un temps d'échange important entre nous, qui nous permet aussi de présenter et discuter nos études. Aussi venez nombreux !!

Amitiés à tous,

François Maccari

Président de Resopso

Sommaire

RESOPSOCAR

« Psoriasis de l'enfant et facteurs de risque cardiovasculaire »

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Résumé

Le psoriasis touche 2 à 4% de la population générale. Les études épidémiologiques montrent qu'environ 1/3 des cas débutent dans l'enfance (jusqu'à 2/3 dans les formes familiales).

Depuis une dizaine d'années, il a été clairement démontré que le psoriasis chez l'adulte est associé de façon significative au syndrome métabolique et à une augmentation de la fréquence des facteurs de risque cardio-vasculaire, en général : HTA, obésité, diabète, tabagisme, alcoolisme, accidents cardiovasculaires majeurs (AVC, angor, IDM) ainsi qu'à une surmortalité cardiovasculaire.

Les études sur le lien entre psoriasis de l'enfant et facteurs de risque cardiovasculaire sont rares et contradictoires :

- Une étude récente (de Jager M, et al. JEADV 2010), suggère sur la base d'un questionnaire adressé aux patients de l'association de patients psoriasiques néerlandais (taux de réponse faible : 1/3) qu'un début précoce du psoriasis n'est pas associé à une obésité à l'âge adulte. Les autres pathologies du syndrome métabolique n'ont pas été inclues dans cette étude.
- Une étude allemande suggère que les enfants atteints de psoriasis seraient plus souvent hypertendus, diabétiques, dyslipidémiques, ou victimes d'accidents vasculaires sévères que les enfants non atteints de psoriasis (Augustin M, et al. BJD 2010)

Nous souhaitions donc évaluer le lien entre début du psoriasis dans l'enfance et facteurs de risque cardiovasculaire (incluant le syndrome métabolique) à l'âge adulte.

L'objectif principal de ce travail était de rechercher si un début précoce du psoriasis, dans l'enfance, est prédictif ou protecteur pour les facteurs de risque cardiovasculaire à l'âge adulte.

Les objectifs secondaires étaient : évaluer la prévalence des facteurs de risque cardio-vasculaire et du syndrome métabolique dans la population psoriasique française ; analyse en sous-groupes : en fonction du sexe, de l'âge de début (<10 ans / > 10 ans), de la sévérité du psoriasis (évalué sur l'utilisation de traitements généraux), type de psoriasis, antécédents familiaux

Début de l'étude Juin 2011
Fin de l'étude Octobre 2011

Nombre de centres 29
Nombre d'inclusions 2 210

Présentations

4 Saisons de la Dermatologie, Paris, 2012
2012 Dermatology European Faculty Forum Amsterdam, Pays-Bas, 2012
Journées Dermatologiques de Paris, 2012
4th Congress of the Psoriasis International Network-Psoriasis 2013, Paris, 2013
12th World Congress of Pediatric Dermatology, Madrid, Espagne, 2013
Journées Dermatologiques de Paris, 2013
Journées Dermatologiques de Paris, 2014
12th EADV Spring Symposium, Valence, Espagne, 2015
28ème Congrès Français de Rhumatologie, Paris, 2015

Publications

Mahé E, Maccari F, Beauchet A, Lahfa M, Barthelemy H, Reguiaï Z, Beneton N, Estève E, Chaby G, Ruer-Mulard M, Steiner HG, Pauwels C, Avenel-Audran M, Goujon-Henry C, Descamps V, Begon E, Sigal ML, for the GEM Resopso. Childhood onset psoriasis: association with future cardiovascular and metabolic comorbidities. *Br J Dermatol* 2013;169:889-95.

Descamps V, Mahé E, Maccari F, Begon E, Barthelemy H, Reguiai Z, Bénéton N, Estève E, Chaby G, Ruer-Mulard M, Steiner HG, Thomas-Beaulieu D, Avenel-Audran M, Goujon-Henry C, Sigal ML, Ezzedine K, Beauchet A. Severe androgenetic alopecia as a proxy of metabolic syndrome in male psoriatic patients older than 59 years. *Eur J Dermatol* 2014;24:356-60.

Phan C, Sigal ML, Estève E, Reguiai Z, Barthélémy H, Bénéton N, Maccari F, Lahfa M, Thomas-Beaulieu D, Le Guyadec T, Vermersch-Langlin A, Mery-Bossard L, Pallure V, Kemula M, Labeille B, Beauchet A, Mahé E, and the GEM RESOPSO. Psoriasis in the elderly: epidemiological and clinical aspects, and evaluation of patients with very late onset psoriasis. *J Eur Acad Dermatol Venereol* 2016;30:78-82.

Phan C, Sigal ML, Lhafa ML, Barthélémy H, Maccari F, Estève E, Reguiai Z, Perrot JL, Chaby G, Maillard H, Bégon E, Alexandre M, Toussaint P, Bastien-Jacquin M, Bravard P, Sauque E, De Quatrebarbes J, Pfister P, Beauchet A, Mahé E, et le GEM Resopso. Comorbidités métaboliques, tabagisme et hypertension artérielle dans le psoriasis en France. Comparaisons aux bases de données nationales. *Ann Dermatol Venereol* 2016;143:264-274.

Publication soumise

Galezowski A, Maccari F, Hadj-Rabia S, Sigal ML, Phan A, Lahfa M, Bursztejn AC, Barthelemy H, Boralévi F, Reguiai Z, Chiaverini C, Estève E, Bourrat E, Ruer-Mulard M, Beauchet A, Mahé E, the *GEM Resopso*, and the *Groupe de Recherche de la Société Française de Dermatologie Pédiatrique*. Psoriasis arthritis in France, from infants to the elderly. Data from two cross-sectional, multicentre studies. *Eur J Dermatol*

Mémoires et thèses

AGNES GALEZOWSKI

Faculté de Médecine Paris VI – Université Pierre et Marie Curie. Thèse de Doctorat en Médecine, spécialité Dermatologie – Vénéréologie. Soutenance : 1er avril 2016

« EPIDEMIOLOGIE DU RHUMATISME PSORIASIQUE EN FRANCE, DE L'ENFANT A LA PERSONNE AGEE. DONNEES DE DEUX ETUDES TRANSVERSALES FRANÇAISES, DANS UNE POPULATION DE PATIENTS ATTEINTS DE PSORIASIS CUTANE »

CELINE PHAN

Mémoire de DES de Dermatologie-Vénéréologie. Région Ile de France. Soutenance : 16 septembre 2016

« PSORIASIS IN THE ELDERLY: EPIDEMIOLOGICAL AND CLINICAL ASPECTS, AND EVALUATION OF PATIENTS WITH VERY LATE ONSET PSORIASIS »

RESOSWITCH

« Etude des changements d'une biothérapie par une autre pour le traitement du psoriasis »

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Résumé

Introduction : Le remplacement d'une 1ère ligne de biothérapie (BT) est une problématique fréquente. Les objectifs principaux de cette étude étaient de déterminer la fréquence et le taux d'efficacité de ces switchs réalisés en pratique courante et de déterminer les facteurs associés à leur réussite.

Matériel et Méthodes : Etude rétrospective multicentrique incluant tous les patients ayant nécessité un changement de leur 1ère BT avant le 31/03/2012 pour le traitement de leur psoriasis. Le recueil de données était réalisé à l'aide d'un questionnaire standardisé. L'échec du switch était défini par l'absence de l'obtention d'un PASI75 après 12 à 16 semaines de traitement et/ou PGA>1. Des analyses univariées et multivariées ont été réalisées.

Résultats : 11 centres français, regroupant 1 157 patients traités par BT ont participé à cette étude (soit environ 20% des patients traités en France pour leur psoriasis). 346 patients ont au moins eu un switch. Leur PASI moyen à l'initiation de la BT était de 18.1 (±10) et 50% des patients avaient un rhumatisme psoriasique. 80% des patients avaient été traités par du methotrexate (MTX), 76% par photothérapie, 31% par de la ciclosporine et 13% par de l'efalizumab. Lors de ce 1er switch, du MTX avait été maintenu en association à la BT pour 15% des patients. Près de la moitié des patients avaient de l'etanercept comme 1ère BT. Le switch le plus fréquent était le remplacement de l'etanercept par l'adalimumab (n=102, soit 31,5% des switchs). Un wash-out avait été respecté dans 47% des cas. La durée moyenne de maintien de la 1ère BT (seule) était de 440 ± 396 jours et de 530 ± 396 jours si du MTX y était associé. Le 1er switch était efficace pour 70% des patients. Les switchs du fait d'une inefficacité initiale (*vs.* intolérance ou échappement thérapeutique) avaient une plus grande fréquence d'échec (p=0,02). Les switchs vers l'ustekinumab étaient significativement associés à une meilleure efficacité (p=0,001). Un 2ème switch avait été réalisé pour 92 patients et considéré comme efficace pour 63% d'entre eux.

Discussion : Aucune caractéristique du patient (âge, sexe, comorbidités, BMI) ou du psoriasis (sévérité, ancienneté, rhumatisme associé, ...) n'influençait l'efficacité du switch. Après un 2ème switch seulement 3% de l'ensemble des patients n'avaient toujours pas trouvé de BT efficace. Le remplacement d'un anti-TNF par de l'ustekinumab était le plus souvent efficace (n=78/88).

Conclusion : Resoswitch est la 1ère étude d'aussi grande envergure, en pratique courante, analysant les switchs d'une 1ère ligne de BT pour le traitement du psoriasis. 30% des 1 136 patients inclus ont nécessité un changement de leur BT. Ceci témoigne de la grande fréquence de cette problématique dont les coûts d'échecs économique et médical sont considérables.

Date de l'étude 2012

Nombre de centres 11
Nombre d'inclusions 346

Présentations *Journées Dermatologiques de Paris, 2013*
5th Congress of the Psoriasis International Network, Paris, 2016

Publication en cours

Dabouz F, Khemis A, Barbe C, Lahfa M, Maccari F, Chaby G, Beneton B, Boye T, Estève E, Mahé E, Bégon E, Pauwels C, Bernard P, Reguiai Z, on behalf of Resopso network. Factors associated with successful switching between biologic therapies for the treatment of psoriasis in daily dermatological real-life practice: the Resoswitch study.

R-ENS

« Resopso : Evaluation Nationale du parcours de Soin pour un psoriasis »

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Résumé

Si le psoriasis est considérée comme bénin, car non mortel, par beaucoup, sa sévérité potentielle et son retentissement sont finalement admis actuellement à plusieurs niveaux :

- physique : certaines formes cliniques présentent un retentissement fonctionnel (acropulpites, psoriasis palmoplantaire par exemple), général (érythrodermie, psoriasis pustuleux), et social (psoriasis du visage, psoriasis unguéal) majeur
- la qualité de vie (QDV) : il n'est plus à démontrer que les différentes dimensions de la qualité de vie sont impactées par le psoriasis (travail, vie familiale, sexualité, ….)
- social : altération des activités collectives, professionnelles, familiales, sportives par exemple
- économique : coût directs (ex : traitements et hospitalisation) et indirects (arrêts de travail, dépressions induites …)
- enfin l'association du psoriasis aux comorbidités métaboliques et cardiovasculaires fait parler par certains auteurs de « maladie systémique ».

Paradoxalement, tant en pratique clinique que dans les données de la littérature, il est montré que :

- une minorité de patients est prise en charge
- la prise en charge des formes sévères est très (trop ?) tardive
- une prise en charge adaptée améliore les différentes dimensions altérées : physique, QDV, social

Peu d'informations sont disponibles pour essayer d'expliquer les raisons de ce retard de prise en charge, où pourquoi les patients tardent tant pour être pris en charge ? S'agit-il de données médicales (par exemple : sous-évaluation du retentissement par le médecin), sociales comme observées pour certaines pathologies comme les cancers ou les maladies cardiovasculaires (rapidité de prise en charge et pronostic corrélé de façon inverse au statut social), individuelles (ex : hommes moins préoccupés par leur apparence que les femmes, …) …

L'objectif de ce travail était de mieux comprendre le parcours des patients psoriasiques avant de consulter un dermatologue adhérent à un réseau de praticiens investis dans la prise en charge du psoriasis, hospitaliers ou libéraux, chez les patients psoriasiques primo-consultants.

Début de l'étude 1er janvier 2013
Fin de l'étude 15 novembre 2013

Nombre de centres 40
Nombre d'inclusions 1 302

Présentations *Journées Dermatologiques de Paris, 2013*
11th EADV Spring Symposium, Belgrade, Serbie, 2014

Publications

Amy de la Bretèque M, Sigal ML, Reguiai Z, Maccari F, Ruer-Mulard M, Le Guyadec T, Estève E, Goujon-Henry C, Chaby G, Barthélémy H, Parier J, Steiner HG, Bégon E, Maillard H, Bastien M, Beauchet A, Mahé E, and the GEM Resopso. Characteristics of patients with plaque psoriasis who have discordance between PASI and DLQI scores. *J Eur Acad Dermatol Venereol 2016 [Epub ahead of print]*

Publications soumises

Mahé E, Maccari F, Beauchet A, Quiles-Tsimaratos N, Beneton N, Parier J, Barthelemy H, Goujon-Henry C, Chaby G, Thomas-Beaulieu D, Géner G, Wagner L, Pallure V, Devaux S, Vermesch-Langlin A, Pfister P, Jégou J, Livideanu C, Sigal ML, pour le GEM Resopso. Patients

atteints de psoriasis : analyse de la population insatisfaite de sa prise en charge. *Ann Dermatol Venereol* Accepté sous réserve de corrections

Mahé E, Beauchet A, Reguiaï Z, Maccari F, Ruer-Mulard M, Chaby G, Le Guyadec T, Estève E, Goujon-Henry C, Parier J, Barthelemy H, Bégon E, Steiner HG, Beneton N, Boyé T, Mery-Bossard L, Schmutz JL, Bravard P, Sigal ML, and the GEM RESOPSO. Socioeconomic inequalities and severity of psoriasis at a first consultation of dermatology. *Acta Derm Venereol* Accepté sous réserve de corrections

METHOPRAC

« Enquête observationnelle multicentrique pour évaluer l'utilisation du METHOtrexate en PRAtique Courante dans le psoriasis en plaques »

Investigateur principal Abdallah Khemis, CHU Larchet, Nice
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Résumé

Rationnel :

- Utilisation croissante du méthotrexate depuis l'émergence des biothérapies
- Aucune étude prospective de grande envergure pour ce médicament incontournable dans le psoriasis
- Absence de recommandation sur l'utilisation optimale du méthotrexate

Objectif principal :

- Efficacité du méthotrexate en terme de PASI 75 à 16 semaines de traitement

Objectif secondaire :

- Efficacité du méthotrexate en terme de PASI 75 à 12 semaines de traitement
- Tolérance en fonction des posologies (15 mg/semaine versus 20 mg/semaine) et des voies d'administration (per os versus sous-cutané)
- Efficacité à la semaine 12 et à la semaine 16 en termes de PASI 50 et PASI 90
- Impact de l'utilisation de la Spéciafoldine®
- Délai de réponse
- Evaluation de la compliance et de l'observance
- Evaluation de l'efficacité et de la tolérance à 6 mois

Début de l'étude janvier 2014
Fin de l'étude février 2015

Nombre de centres 19
Nombre d'inclusions 250

Présentation *Journées Dermatologiques de Paris, 2015*

RESOPSONET

« Patients souffrant de psoriasis et internet »

Investigateur principal Maud Amy de la Bretèque, Hôpital Victor Dupouy, Argenteuil
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Résumé

En France, un peu plus de trois personnes sur quatre ont globalement accès à internet, mais le pourcentage d'internautes dans la population est plus élevé chez les plus jeunes, de 99% chez les 12-17ans à 22% des plus de 70 ans. Selon la revue de la littérature « Le patient internaute », élaborée par la HAS, 1 patient sur 5 environ cherche de l'information médicale et de santé sur Internet. Les résultats de l'enquête Médiamétrie/Net Ratings indiquent par ailleurs que, parmi les 25 sites les plus visités en France au mois de septembre 2007, figurent deux sites Internet santé ou sites disposant d'un espace d'information dédié à l'information santé.

Ces données témoignent de la montée en puissance du média Internet dans le traitement des sujets médicaux et de santé. En effet, les patients n'hésitent plus à multiplier leurs sources d'information santé et à les recouper, y compris sur Internet.

Concernant l'utilisation d'internet chez des patients atteints de psoriasis, des travaux ont été publiés sur l'utilisation des réseaux sociaux. Les auteurs ont montré que ces communautés virtuelles offraient aux utilisateurs à la fois une valeur éducative et un soutien psychologique et social (*Arch Dermatol 2009)*.

Il est légitime de s'interroger sur le profil des patients qui cherchent ce type d'information et sur la qualité de cette information.

L'objectif de cette étude est de décrire les caractéristiques des patients atteints de psoriasis consultant internet, de décrire le contexte et l'impact de ces recherches sur le comportement des patients. Dans un second temps, les sites les plus visités seront analysés avec évaluation des critères de qualité des sites, et de la qualité de l'information médicale.

Début de l'étude 25 août 2014
Fin de l'étude 31 octobre 2014

Nombre de centres 39
Nombre d'inclusions 1115

Présentation *5th Congress of the Psoriasis International Network, Paris, 2016*

Article en préparation

Amy de la Bretèque M, Sigal ML, Maccari F, Barthélémy H, Estève E, Girard C, Maillard H, Avenel-Audran M, Perrot JL, Modiano P, Quiles-Tsimaratos N, Parier J, Bégon E, Pallure V, Becherel PA, Chaby G, Beauchet A, Mahé E, and GEM Resopso. Patients with psoriasis and the Internet: profile of the population consulting websites, and evaluation of the websites.

CIRRHO-BIO

« Etude rétrospective de la tolérance et de l'efficacité des biothérapie dans le psoriasis chez les patients cirrhotiques post alcooliques »

Investigateur principal Edouard Bégon, Hôpital René Dubos, Pontoise
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Résumé

Introduction : La tolérance et l'efficacité des biothérapies du psoriasis dans la population particulière des patients cirrhotiques n'a jamais été étudiée. Cette population n'est pas incluse dans les essais randomisés prospectifs analysant les biologiques du fait de cette comorbidité. Pourtant du fait de la sévérité du psoriasis chez les patients alcooliques, de l'hépatoxicité ou des difficultés d'emploi des autres traitements systémiques conventionnels, de l'absence de contre-indication des biologiques en cas d'insuffisance hépatique les biothérapies ont une place de choix dans le traitement du psoriasis au cours de la cirrhose. Néanmoins les risques infectieux bactériens et le risque d'hépatocarcinome inhérents à la cirrhose invitent à préciser le profil de tolérance de ces molécules au cours de la cirrhose alcoolique.

Objectif : Analyse rétrospective multicentrique observationnelle des événements indésirables (EI) et de l'efficacité (réponse PGA) sous biothérapie (etanercept, adalimumab, infliximab et ustekinumab) chez les patients présentant un psoriasis ± rhumatisme psoriasique et une cirrhose post alcoolique ou cirrhose mixte post alcoolique et stéatohépatite dysmétabolique diagnostiquée par un hépatologue avant introduction du biologique.

Patients et méthodes : Etude rétrospective nationale après appel à cas de tous les centres du Groupe d'Etude Multicentrique (GEM) de RESOPSO (56 centres). Ont été colligés pour chaque patient : âge, sexe, type et gravité (score CHILD) de la cirrhose, durée de la cirrhose avant introduction de la biothérapie, obtention d'un sevrage alcoolique, nature et durée du traitement par biothérapie, EI survenant sous biothérapie et après arrêt jusqu'à 5 demi-vie, efficacité en terme d'obtention d'un score PGA 0 à 1 (blanchiment à quasi blanchiment) à M3, M6 et M12.

Résultats : 23 patients ont été inclus (âge médian : 59 ans ; H/F : 19/4) issus de 15 centres GEM. La durée moyenne d'évolution du psoriasis avant introduction du biologique était de 34 ans et l'ancienneté du diagnostic de la cirrhose de 12 mois (1 à 153 mois). La cirrhose était de gravité légère compensée CHILD A dans 21/23 cas. Seuls 9/23 patients (39%) ont cessé leur intoxication alcoolique durant la période d'étude. Plus de la moitié des patients (14/23) n'avait reçu qu'un systémique conventionnel (photothérapie, acitrétine, méthotrexate, ciclosporine) avant introduction du biologique. Vint trois patients ont reçu 33 lignes de traitements : etanercept : 10 ; adalimumab : 8 ; infliximab : 5 et ustekinumab : 10. Le score PASI moyen avant biothérapie était de 27 et le score PGA moyen de 4. La durée moyenne de traitement par biothérapie était de 22 mois (4-102 mois). La durée moyenne de la cirrhose post alcoolique avant introduction du biologique était de 12 mois (1-153 mois). Cinq patients ont présenté un EI sous biologique : 1 patient un érysipèle de jambe à 5 mois d'infliximab, 1 patient un érysipèle de jambe à 4 mois d'infliximab, 1 patient deux épisodes d'érysipèle de jambe à 1 mois et à 21 mois d'etanercept, 1 patient une pneumopathie infectieuse non sévère à 7 mois d'etanercept, 1 patient grabataire érythrodermique décédé sous ustekinumab de sepsis dans un contexte de cirrhose CHILD C. Aucune infection tuberculeuse, infection opportuniste, infection de liquide d'ascite ou hépatocarcinome n'était observé. Un blanchiment ou quasi blanchiment (score PGA O à 1) était constaté chez 7/23 patients (30%) à la semaine 16, chez 13/21 (62%) à la semaine 24 et chez 14/17 (82%) à un an de traitement.

Conclusion : Malgré l'augmentation du risque infectieux et carcinologique lié à la cirrhose alcoolique la tolérance des biothérapies du psoriasis apparaît satisfaisante dans cette série rétrospective de 23 patients cirrhotiques présentant un psoriasis sévère traités en moyenne plus de deux ans. Les biothérapies sont efficaces malgré l'alcoolisation poursuivie permettant un blanchiment ou quasi blanchiment chez 62 à 82% des patients entre 6 mois et un an. Du fait des difficultés d'emploi des autres traitements systémiques conventionnels les biologiques ont une place dans cette population particulière.

Début de l'étude	septembre 2014
Fin de l'étude	août 2015
Nombre de centres	15
Nombre d'inclusions	21
Présentation	*Journées Dermatologiques de Paris, 2015* *5th Congress of the Psoriasis International Network, Paris, 2016*

RESOPSO SENIOR

*« **S**afety and efficacy of biologic treatments in **E**lderly patie**N**ts with psor**I**asis: a multicenter nati**O**nal ret**R**ospective study »*

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Résumé

L'étude a pour objectifs :

Objectif primaire :
Etude la tolérance des biologiques chez patients atteints de psoriasis de plus de 65 ans (inclus)

Objectifs secondaires :
Etude de l'efficacité des biologiques chez ces patients
Description des caractéristiques phénotypiques du psoriasis et les comorbidités

Critères d'inclusion :

Inclusion des patients ayant 65 ans ou plus lors de l'initiation ou survenant au cours d'un traitement par biologique prescrit pour un psoriasis cutané : étanercept, adalimumab, infliximab, ustekinumab. Il peut s'agir de patients naïfs ou non de biologiques antérieurs.

Nombre de centres 10
Nombre d'inclusions 41

Début de l'étude 30 septembre 2014
Fin de l'étude 31 janvier 2016

Présentation *Journées Dermatologiques de Paris, 2015*
5th Congress of the Psoriasis International Network, Paris, 2016
25th EADV Congress, Vienne, Autriche, 2016

ECHELLE SKIN CAT

« Contraintes Associées au Traitement »

Création d'un questionnaire patient évaluant
les contraintes associées au traitement du psoriasis

Investigateur principal Edouard Begon, Hôpital René Dubos, Pontoise
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Groupe projet SKIN CAT : Marie Bastien (Cabinet Val de Marne), Hugues Barthelemy (Cabinet CH Auxerre), Alain Beauchet (CHU Ambroise Paré – URC), Catherine Goujon (CHU Lyon), Bruno Halioua (Cabinet Paris), Caroline Jacobzone (CH Lorient), François Maccari (HIA Begin), Laurent Wagner (Cabinet Paris)

Partenaires de l'étude

Société de recherche clinique médicale (interview patients etc..): NUKLEUS
Unité de Recherche Clinique (URC), hôpital Ambroise Paré (Alain Beauchet)

Financeur de l'étude

RESOPSO au travers d'un budget alloué par le laboratoire Cellgene à hauteur de 109 375 €, après acceptation de cette sollicitation de financement par le laboratoire, selon les devis émis par la société Nukleus et l'URC Ambroise Paré, en contrepartie de la libre utilisation par le laboratoire Cellgene de l'échelle SKIN CAT dans les études promues par Cellgene. RESOPSO est seul promoteur de l'étude et propriétaire de l'ensemble des données

Résumé

L'objectif du projet est la création d'un questionnaire patient à type d'échelle de quantification visant à évaluer le fardeau du traitement (Treatment burden) / les contraintes liées au traitement (CAT ou Contraintes Associées aux Traitements) chez les patients psoriasiques en France. Cette échelle à la manière du score DLQI comprendra entre 10 et 15 questions. Notre objectif est de cerner au plus près le fardeau thérapeutique de chaque traitement en concentrant le questionnaire sur ce point particulier et en mettant de côté l'efficacité et les effets secondaires. Les patients psoriasiques seront au cœur de l'élaboration de cette échelle afin de distinguer au mieux les aspects prédominants de cette contrainte dans la vie courante. A terme cette échelle sera un nouvel outil de mesure pour le choix de thérapeutiques au profil similaire de tolérance / efficacité mais dont les contraintes peuvent être très différentes. Ce questionnaire sera élaboré à partir d'interview de patients psoriasiques d'âge, de profession, de sévérité de maladie et de traitement différents dans l'objectif de couvrir le panel le plus large possible des contraintes vécues dans tous les aspects de la vie.

Après une étape de choix des items les plus pertinents pour répondre à l'objectif de mesure ce questionnaire sera évalué au travers d'une étude large sur plusieurs centaines de patients.

Déroulement de l'étude

Etape 1 : phase qualitative d'élaboration des items de l'échelle SKIN CAT (année 2016)

1-1 Etape qualitiative interview

. Identification des items devant faire partie de l'échelle grâce aux interviews d'une trentaine de patients psoriasiques + 2 focus groupe de 4 à 5 dermatologues de RESOPSO (hors groupe Skin CAT) + interview de deux généralistes

. Le groupe SKIN CAT recrute les patients et fait appel aux collègues de RESOPSO pour participer aux interviews.

1-2 Etape d'élaboration des items de l'échelle SKIN CAT

. Première version de l'échelle SKIN CAT

1-3 Etape Delphi

. Dix experts dermatologues (membres GEM) sont interrogés par courriel sur le contenu et la pertinence des items selon la méthode DELPHI (à l'aide d'une échelle de cotation de Likert)

. Le groupe SKIN CAT détermine selon ces réponses une première version de SKIN CAT (SKIN CAT 1)

1-4 Etape de vérification effets seuil / plafond

. Elaboration de la version SKIN CAT 2

1-5 Valorisation / publication

. Une première publication en anglais présentant l'échelle SKINCAT et la méthodologie d'élaboration sera soumise. La liste des auteurs comprendra : Edouard BEGON (premier auteur), Alain Beauchet (dernier auteur), l'ensemble des dermatologues du groupe SKINCAT (ordre à définir), les collègues de la société Nukleus, GEM RESOPSO. L'échelle et son nom seront déposés à l'Institut National de la Propriété Intellectuelle

Etape 2 : validation quantitative à grande échelle (analyse des propriétés psychométriques) (année 2016-2017)

. Un échantillon de 250 patients sera constitué

. Tous les centres du GEM RESOPSO seront appelés à inclure des patients

. Seront inclus des patients psoriasiques âgés de plus de 18 ans ayant un traitement stable depuis plus de 6 mois et dont le traitement n'est pas modifié à l'issue de la consultation

. Tous les patients complèteront le SKIN CAT 2 et en parallèle le questionnaire de satisfaction sur les traitements à base de médicaments (TSQM version II) ; sur la fiche apparaîtra les initiales du patient (N/P) et le numéro du centre

. Tous les patients inclus devront remplir à domicile une seconde fois entre 15 jours et un mois le questionnaire SKIN CAT 2 et le retourner par enveloppe, ceci pour vérifier la reproductibilité dans le temps du questionnaire (méthode du test / retest)

. Le CRF de l'étude sera court

. Les CRF, les fiches 1 SKIN CAT et le TSQM seront adressés par les membres GEM RESOPSO à Alain Beauchet par courrier ou fax

. Les fiches 2 SKIN CAT remplies par le patient à domicile seront adressées à Alain Beauchet URC Ambroise Paré par courrier avec enveloppe préaffranchie

. La saisie de données sera effectuée par l'URC Ambroise Paré et Alain Beauchet effectuera l'analyse statistique des données

. Une seconde publication en anglais présentant l'échelle et la méthodologie de validation sur un large échantillon de patients sera soumise

PSOLIB

« Enfants psoriasiques consultant en cabinet libéral : aspects cliniques, thérapeutiques et comorbidités »

Investigateur Emmanuel Mahé, Hôpital Victor Dupouy, Argenteuil
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Résumé

Introduction. Le psoriasis touche 0,5 à 0,7% des enfants en Europe. Depuis plusieurs années, les données s'accumulent sur l'épidémiologie, les comorbidités, les aspects cliniques et thérapeutiques du psoriasis chez l'enfant. Ces grandes études s'appuient soit sur des études de registres le plus souvent déclaratifs sans contrôle clinique des diagnostics (assurances, données d'associations de patients) soit sur des travaux hospitaliers. Aucune étude n'a été réalisée en cabinet de dermatologie libéral, premier passage auprès de la dermatologie de ces enfants.

Objectif. L'objectif de ce travail est de définir la fréquence des comorbidités (surpoids / obésité) chez les enfants atteints de psoriasis, en pratique courante de ville. Ce travail permettra aussi de mieux définir les aspects cliniques, et les aspects thérapeutiques des enfants atteints de psoriasis, et vus en ville

Matériel et méthodes. Etude transversale, multicentrique (recrutement par la FFCEDV de 50 dermatologues libéraux), avec inclusions consécutives de tous les enfants (< 18 ans) atteints de psoriasis (diagnostic certain). Questionnaire standardisé analysant les aspects cliniques, la sévérité, les traitements utilisés, et les comorbidités (essentiellement étude du surpoids et de l'obésité). L'étude durera 1 an, l'objectif est d'inclure 250 à 300 enfants. Les données seront comparées aux données de l'étude χ-psocar (310 enfants psoriasiques français issus d'un recrutement hospitalier).

Résultats espérés, perspectives. Cette étude permettra de mieux cerner le profil des enfants psoriasiques vus en ville (majorité des enfants), de mieux définir le biais potentiel des recrutements hospitaliers, et par conséquent de mieux adapter notre prise en charge (identification des besoins, cibles de la formation) des enfants atteints de psoriasis.

Collaboration FFFCEVD – GEM Resopso
Début de l'étude Mai 2016
Fin de l'étude : Mai 2017

Nombre de centres 38
Nombre d'inclusions 68 (en cours)

ALTERNATIVE

« Utilisation des médecines dites « alternatives » ou « douces »
dans la prise en charge du psoriasis »

Investigateurs Molka Ariane, Emmanuel Mahé, Hôpital Victor Dupouy, Argenteuil
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Résumé
Le dermatologue est souvent mal à l'aise pour conseiller à ses patients d'éventuelles médecines alternatives (régimes, homéopathie, ichtyothérapie, …), pour des raisons de méconnaissance de ces thérapeutiques, mais aussi souvent par conviction scientifique. Si ces thérapeutiques ont rarement montré leur efficacité sur la prise en charge des dermatoses chroniques inflammatoires, elles peuvent être appréciées par certains patients et avoir un effet sur la dermatose et le bien-être de celui-ci.
Une étude récente (Albert C, et al. 28ème Congrès Français de Rhumatologie 2015) portant sur l'utilisation des régimes d'éviction alimentaires réalisée auprès de 382 patients atteints de rhumatismes a montré que :

- 23% des patients avaient essayé un régime d'éviction
- Le régime était sans effet sur le rhumatisme
- Et le régime était conseillé par 59% des patients l'ayant utilisé !

Cette étude consolide le « scientifique » mais illustre aussi le besoin des patients d'essayer d'autres voies, qui à défaut d'être efficaces semblent appréciées.
L'objectif de ce travail est d'évaluer la fréquence d'utilisation des thérapeutiques alternatives, et notamment des régimes alimentaires (le questionnaire princeps a été adressé par le Dr Albert, rhumatologue à Nice), chez les patients souffrant de psoriasis, et le profil de ces patients. Les résultats seront source de réflexion sur nos pratiques et seront discutés lors de la session de FMC des JDP 2016 (J.-L. Schmutz, H. Maillard, E. Mahé) traitant de ce sujet.

Début de l'étude 1er Juin 2016
Fin de l'étude 15 septembre 2016

Nombre de centres 15
Nombre d'inclusions 584

INIBIO 1

« Profil des patients psoriasiques à l'initiation d'une biothérapie »

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Résumé
Les biothérapies (ant-TNF-alpha et anti-IL12/23) sont utilisées depuis de nombreuses années dans le psoriasis en plaques. Leur AMM est très voisine et le choix de l'initiation d'un traitement plutôt qu'un autre porte sur des critères « personnels » : association à un rhumatisme psoriasique, comorbidités, expérience personnelle, conflits d'intérêt … qui s'appuient sur des données scientifiques mais aussi de lobbying de l'industrie.
L'objectif de ce travail est d'évaluer le profil des patients à l'introduction d'une biothérapie afin de préciser quels sont les critères qui conditionnent, en vie réelle, nos choix. Ces résultats seront source de réflexion sur nos pratiques et probablement pourront être discuté lors de formations Resopso (et évidemment pourront avoir un impact pour les industriels).
Il est prévu de réaliser ce travail tous les 2 ans afin de suivre l'évolution des profils des patients recevant des biothérapies avec l'arrivée des nouvelles classes de biothérapies et l'arrivée des biosimilaires.

Début de l'étude Juillet 2016
Fin de l'étude Octobre 2016

Nombre de centres 15
Nombre d'inclusions 215

Etudes abouties

RESOPSO-PI - *« Psoriasis : prise de Poids sous Infliximab » (2012)*
Investigateur principal : Emmanuel Mahé, Hôpital Victor Dupouy, Argenteuil
Présentation : *4th Congress of the Psoriasis International Network - Psoriasis 2013, Paris, 2013*
Publication :
Mahé E, Reguiai Z, Barthelemy H, Quiles-Tsimaratos N, Chaby G, Girard C, Estève E, Maccari F, Descamps V, Schmutz JL, Begon E, Bravard P, Maillard H, Boyer T, Beauchet A, Sigal ML, for the GEM Resopso. Evaluation of risk factors for body weight increment in psoriatic patients on infliximab: a multicentre, cross-sectional study. *J Eur Acad Dermatol Venereol* 2014;28:151-9.

VITIBIO - *« Apparition ou modification d'un VITIligo sous BIOthérapie » (2013-14)*
Investigateur principal : Laure Méry-Bossard, CH François Quesnay, Mantes la Jolie
Présentations : *26ème Congrès Français de Rhumatologie, Paris, 2013 ; EULAR 2014/ ACR, Paris, 2014 ; Journée Dermatologiques de Paris, 2014 ; 27ème Congrès Français de Rhumatologie, Paris, 2014 ; 24th EADV Congress, Copenhague, Danemark, 2015*
Publication :
Méry-Bossard L, Bagny K, Chaby G, Khemis A, Macarri F, Sigal ML, Marotte F, Perrot JL, Reguiai Z, Avenel-Audran M, Boyé T, Grasland A, Gillard J, Jullien D, Quiles N, Sibilia J, Bastien M, Beneton N, Benmansour A, Carbonnel F, Collet P, Descamps V, Gaudin P, Jacobzone C, Parier J, Toussirot E. New-onset vitiligo and progression of pre-existing vitiligo during treatment with biological agents in chronic inflammatory diseases. *J Eur Acad Dermatol Venereol* 2016 Jun 13. doi: 10.1111/jdv.13759. [Epub ahead of print]

MGUS - « Apparition de gammapathies monoclonales dans le psoriasis sous biothérapie » (2013-14)
Investigateurs principaux : Anne-Laure Liégeon, Jean-Luc Schmutz, CHU Nancy, Vandœuvre-Les-Nancy
Présentation : *Journées Dermatologiques de Paris, 2014*
Publication :
Liégeon AL, Mahé E, Bégon E, Poreaux C, Barbaud A, Esteve E, Quiles-Tsimaratos N, Avenel-Audran M, Schoeffler A, Mery-Bossard L, Pauwels C, Girard C, Maillard H, Barthelme D, Bernier C, Chaby G, Reguiai Z, Nguyen-Thi PL, Maccari F, Schmutz JL. Development of monoclonal gammopathy under biotherapy in psoriasis: a French multicenter retrospective study. *Eur J Dermatol* 2016:26;75-81.
Mémoire de DES de Dermatologie et Vénéréologie
Anne-Laure Liégeon. Faculté de Médecine de Nancy, Université de Lorraine. « Apparition de gammapathies monoclonales sous biothérapie dans le psoriasis : étude rétrospective multicentrique française ». Direction : Jean-Luc Schmutz. Soutenance : Octobre 2014

« Psoriasis induits par les anti-PD1 » (2015)
Investigateur principal : Emmanuel Mahé, Hôpital Victor Dupouy, Argenteuil
Présentations : *5th Congress of the Psoriasis International Network, Paris, 2016 ; Journées Dermatologiques de Paris, 2016 ; 10ème Journée Scientifique Annuelle du Groupe de Recherche sur le Psoriasis*
Publication :
Bonigen J, Raynaud C, Hureaux J, Kramkimel N, Blom A, Jeudy G, Breton AL, Hubiche T, Bedane C, Legoupil D, Pham-Ledard A, Pérol M, Gérard E, Combemale P, Bonnet D, Sigal ML, Mahé E, for the *Groupe de Recherche sur le Psoriasis* and the *Groupe Cancérologie Cutanée* of the *Société Française de Dermatologie*, the *GEM Resopso*, *Apsoderm*, the *CEDEF*, and the *Groupe Français de Pneumo-Cancérologie*. Anti-PD1-induced psoriasis. A study of 21 patients. *J Eur Acad Dermatol Venereol* 2017 [Epub ahead of print]

Présentations aux congrès (2016)

5TH CONGRESS OF THE PSORIASIS INTERNATIONAL NETWORK, PARIS, 2016

SAFETY AND EFFICACY OF BIOLOGIC THERAPIES IN PSORIATIC PATIENTS WITH ALCOHOLIC CIRRHOSIS: A FRENCH RETROSPECTIVE STUDY OF 23 CASES
Begon E, Beneton N, Poiraud C, Droitcourt C, Jacobzone C, Vermersch-Langlin A, Descamps V, Perrot JL, Khemis A, Pallure V, Fougerousse AC, Sigal ML, Goujon C, Avenel M, Schmutz JL, Reguiai Z, GEM Resopso

PSORIASIS IN THE ELDERLY PATIENTS IN FRANCE
Beneton N, Mahé E, Bauchet A, Chaby G, Quiles N, Pallure V, Khemis A, Maccari F, Begon E, Boyé T, and Resopso.

FACTORS ASSOCIATED WITH SUCCESSFUL SWITCHING BETWEEN BIOLOGIC THERAPIES FOR THE TREATMENT OF PSORIASIS IN DAILY DERMATOLOGICAL REAL-LIFE PRACTICE. THE RESOSWITCH STUDY.
Dabouz F, Khemis A, Lahfa M, Maccari F, Chaby G, Beneton N, Boyé T, Esteve E, Mahé E, Begon E, Pauwels C, Bernard P, Reguiai Z, and Resopso.

ANTI-PD1-INDUCED PSORIASIS. A CASE SERIES
Bonigen J, Raynaud C, Hureaux J, Kramkimel N, Blom A, Jeudy G, Breton AL, Hubiche T, Bedane C, Legoupil D, Pham-Ledard A, Pérol M, Gérard A, Combemale P, Bonnet D, Sigal ML, Mahé E, for the *Groupe de Recherche sur le Psoriasis* and the *Groupe Cancérologie Cutanée* of the *Société Française de Dermatologie*, the *GEM Resopso*, *Apsoderm*, the *CEDEF*, and the *Groupe Français de Pneumo-Cancérologie*

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Amy De La Bretêque M, Sigal ML, Maccari F, Barthélémy H, Esteve E, Girard C, Maillard H, Avenel-Audran M, Perrot JL, Modiano P, Quikes-Tsimaratos N, Parier J, Begon E, Pallure V, Becherel PA, Chaby G, Beauchet A, Mahé E, GEM Resopso

25TH EADV CONGRESS, VIENNE, AUTRICHE, 2016

PRELIMINARY RESULTS OF A MULTICENTER RETROSPECTIVE STUDY ON THE USE OF BIOLOGICAL THERAPIES IN ELDERLY PATIENTS FOR PSORIASIS.
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Bonigen J, Raynaud-Donzel C, Hureaux J, Kramkimel N, Blom A, Jeudy G, Breton AL, Hubiche T, Bedane C, Legoupil D, Pham-Ledard A, Pérol M, Gérard E, Combemale P, Bonnet D, Sigal ML, Mahé E et Groupe de Recherche sur le Psoriasis (GrPso) et Groupe Cancérologie Cutanée (GCC) de la Société Française de Dermatologie, GEM Resopso, Apsoderm, CEDEF, et le Groupe Français de Pneumo-Cancérologie

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Bonigen J, Raynaud-Donzel C, Hureaux J, Kramkimel N, Blom A, Jeudy G, Breton AL, Hubiche T, Bedane C, Legoupil D, Pham-Ledard A, Pérol M, Gérard E, Combemale P, Bonnet D, Sigal ML, Mahé E et Groupe de Recherche sur le Psoriasis (GrPso) et Groupe Cancérologie Cutanée (GCC) de la Société Française de Dermatologie, GEM Resopso, Apsoderm, CEDEF, et le Groupe Français de Pneumo-Cancérologie

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British Journal of Dermatology 2013;169:889-95.

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Mahé E, Reguiai Z, Barthelemy H, Quiles-Tsimaratos N, Chaby G, Girard C, Estève E, Maccari F, Descamps V, Schmutz JL, Bégon E, Bravard P, Maillard H, Boyer T, Beauchet A, Sigal ML, for the *GEM Resopso*
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European Journal of Dermatology 2014;24:356-60.

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Phan C, Sigal ML, Estève E, Reguiai Z, Barthélémy H, Bénéton N, Maccari F, Lahfa M, Thomas-Beaulieu D, Le Guyadec T, Vermersch-Langlin A, Mery-Bossard L, Pallure V, Kemula M, Labeille B, Beauchet A, Mahé E, and the *GEM RESOPSO*
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Liégeon AL, Mahé E, Bégon E, Poreaux C, Barbaux A, Estève E, Quiles-Tsimaratos N, Avenel-Audran M, Schoeffler A, Mery-Bossard L, Pauwels C, Girard C, Maillard H, Barthelme D, Bernier C, Chaby G, Reguiai Z, Nguyen-Thi PL, Maccari F, Schmutz JL.
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METABOLIC COMORBIDITIES AND HYPERTENSION IN PSORIASIS PATIENTS IN FRANCE. COMPARISONS WITH FRENCH NATIONAL DATABASES.
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Annales de Dermatologie et Vénéréologie *2016*;143:264-74.

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Mahé E, Beauchet A, Reguiaï Z, Maccari F, Ruer-Mulard M, Chaby G, Le Guyadec T, Estève E, Goujon-Henry C, Parier J, Barthelemy H, Bégon E, Steiner HG, Beneton N, Boyé T, Mery-Bossard L, Schmutz JL, Bravard P, Sigal ML, and the GEM RESOPSO.
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European Journal of Dermatololgy

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Development of monoclonal gammopathy under biotherapy in psoriasis: French multicenter retrospective study

Introduction: Biotherapies or targeted therapies are fairly new treatments indicated for moderate to severe psoriasis. The side effects appear to be mainly infectious or cancerous. The role of biotherapies in the development of a pre-cancerous condition, monoclonal gammopathy of undetermined significance (MGUS), has recently been debated in the literature. The objective of our study was to evaluate the incidence of MGUS in psoriasis patients treated with biotherapy. *Materials and methods:* This study was a French multicenter retrospective study carried out through the French multicenter study group RESOPSO. Data on the results of serum protein electrophoreses performed before and within at least 6 months after the start of the biotherapy were collected. Demographic data, medical history, and psoriasis treatment history were specified. *Results:* Four hundred and forty three patients were eligible for inclusion. Of these, three presented with monoclonal gammopathy for which the assessment was in favor of MGUS. The average treatment period was 19.7 months. Six patients presented with MGUS prior to the treatment. These patients' immunoglobulin levels remained stable, with an average remission of 24 months. Only psoriatic rheumatism appeared to be statistically linked to MGUS. *Conclusion:* The incidence and frequency of MGUS in psoriasis patients treated with biotherapy do not appear to increase relative to the general population.

Key words: biotherapy, monoclonal gammapathy, psoriasis

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Psoriasis is a common chronic inflammatory disease that alters the quality of life of patients who have it. Targeted therapies or biotherapies based on a better understanding of the physiopathology of psoriasis have been developed in the last 10 years. The main side effects appear to be infectious or cancerous. Several studies have suggested that these novel therapies may be responsible for the development of monoclonal gammopathy [1-4]. The main etiological form is monoclonal gammopathy of undetermined significance (MGUS), in which the risk of progression to multiple myeloma increases over time. For example, Prignano *et al.* [1, 2] reported 12 MGUS cases out of 202 psoriasis patients treated with biotherapy, Vilarrasa *et al.* [3] reported 2 MGUS cases out of 307, and Di Lernia *et al.* [4] reported 8 MGUS cases out of 140 such patients. However, the exact physiopathology underlying the development of MGUS is unknown [5]. MGUS is defined as a proliferation of cells with a monoclonal protein level below 3 g/dL, less than 10% plasma cells in the marrow and no impairment of other organs. The discovery of monoclonal gammopathy may also be linked to Waldenström's disease, multiple myeloma, lymphoma, chronic lymphoid leukemia or amyloidosis, thus underscoring the importance of early detection, which in turn permits early treatment. The objective of the present study was to evaluate the incidence of the development of monoclonal gammopathy in psoriasis patients treated with biotherapy.

Materials and methods

The study was multicenter, retrospective, voluntary and organized through the Multicenter Study Group (*Groupe d'Etudes Multicentriques* (GEM)) of RESOPSO (a French association of dermatologists for the optimization of psoriasis care). GEM is the umbrella organization of more than 40 hospital or private medical care centers throughout France. The questionnaires were completed by the attending doctor on the basis of the data in the medical file and in accordance with the frequency of consultations and when the serum protein electrophoreses (SPE) were performed. Information on demographics (age, gender, profession, and tobacco and alcohol consumption), history of high blood pressure, dyslipidemia, diabetes, the clinical type of psoriasis, the association with rheumatism and prior treatments was collected. The biotherapy data were used to quantify the prescription period as well as the dose regime of each molecule. Data on pretreatment SPE and SPE performed at least within 6 months after the start of the treatment were recorded.

If polyclonal hypergammaglobulinemia was discovered, supplemental information on the inflammatory assessment was requested (ESR, CRP) and the search for an etiology was proposed. If monoclonal gammopathy was discovered, information on the assessment performed was requested. This information was used to determine whether the patients presented with tumor syndromes (adenopathy, hepatosplenomegaly), abnormal test results (urinary, blood, and kidney test results, calcemia, LDH, beta-2-microglobulin, albuminemia, myelogram, bone marrow biopsy), or abnormal imaging results (cervico-thoraco-pelvic scan). These elements were used to propose an etiology for the monoclonal hypergammaglobulinemia (MGUS, multiple myeloma, primitive amyloidosis, non-Hodgkin's malignant lymphoma, chronic lymphoid leukemia or Waldenström's disease).

Table 1. Clinical characteristics of the patients

Type of psoriasis	Number (Percentage / 443 patients)
Plaque	390 (88%)
Guttate	29 (6.5%)
Inverse	10 (2.3%)
Nail	23 (5.2%)
Scalp	24 (5.4%)
Pustular	13 (2.9%)
Palmoplantar	27 (2.7%)
Erythrodermic	12 (2.7%)
Psoriatic rheumatism	119 (26.9%)

The inclusion criteria were as follows: adult patient; with any clinical form of cutaneous psoriasis (plaque, guttate, nail, pustular, inverse, erythrodermic, of the scalp, palmoplantar, psoriatic rheumatism); having received or currently undergoing biotherapy (efalizumab, infliximab, etanercept, adalimumab or ustekinumab) for at least 6 months; and in whom an SPE was performed after more than 6 months of treatment. A pre-treatment SPE performed in the year before the initiation of treatment was required in the event of a pathologic SPE under treatment. The exclusion criteria were as follows: patients with known histories of Waldenström's disease, multiple myeloma, lymphoma, amyloidosis or chronic lymphoid leukemia.

Means, medians, and standard deviations were calculated to analyze the quantitative data. The analyses for comparing the different groups of results were performed using Fisher tests for the qualitative data and the Kruskal-Wallis test for the quantitative data. A value of $p < 0.05$ was considered statistically significant.

The number of subjects needed was calculated on the basis of previous studies. The prevalence of MGUS under biotherapy is around 3%; the prevalence in the general population is also about 3%. With an alpha risk of 0.05% and a precision of 1%, the minimum number of patients would be 380. Given that the number of psoriasis patients treated by the participating centers is more than 500 annually and taking into account the number of patients lost to follow-up, the present study included all of the eligible patients seen at our centers for a period of about 1 year, or at least 400 patients.

Results

A total of 465 data collection sheets were received, out of which 443 were usable for this study. The presence of hypergammaglobulinemia after the start of treatment without pretreatment SPE was the reason for not including these 22 sheets. The mean age was 48.7 years and 59.6% of the patients were male. Plaque psoriasis was the predominant clinical form of psoriasis (88%). Psoriatic rheumatism was involved in 26.9% of the cases *(table 1)*. The treatment history data are summarized in *table 2*.

Psoriasis progressed over 18.9 ± 12.3 years on average (median: 17 years; minimum: 1 year; maximum: 58 years).

Table 2. Treatment history

Treatment	N (%)
Treatments received	
UVB TL01	168 (3.9)
PUVA therapy	266 (60.0)
RetiPUVA	17 (3.8)
Methotrexate	358 (80.8)
Acitretin	234 (52.8)
Cyclosporine	158 (35.7)
Efalizumab	19 (4.3)
Infliximab	122 (27.5)
Etanercept	200 (45.1)
Adalimumab	212 (47.9)
Ustekinumab	191 (43.1)
Biotherapy in course	
None	11 (2.5)
Infliximab	55 (12.4)
Etanercept	85 (19.2)
Adalimumab	14 (25.7)
Ustekinumab	178 (40.2)

The average period of SPE monitoring was 32.2 ± 25.4 months, (median: 24 months; minimum: 6 months; maximum: 163 months). Out of 443 patients, 9 (2%) presented with MGUS before or after the treatment. Three (mean age 57.7 years) developed monoclonal gammopathy under biotherapy (*tables 3, 4*). Of these three patients, the treatment was stopped in one of them and regression of the monoclonal gammopathy was observed. The monoclonal immunoglobulin (Ig) was an IgG kappa in two cases and an IgG lambda in one case. The Ig level was non-quantifiable in two cases. The etiologic assessment was in favor of MGUS in these three patients, and the systemic assessment was normal. It took 42, 7, and 10 months after the start of biotherapy for MGUS to develop in these three patients, respectively.

On the other hand, six patients presented with monoclonal gammopathy prior to the initiation of biotherapy. The mean age of these patients was 59.9 years. Three presented with an IgG kappa, two with an IgA kappa, and one with an undetermined IgA. SPE monitoring of these patients was performed between 7 and 62 months, with a mean of 24 months (*table 5*). The Ig level was not determined in two cases and remained stable in the other four cases.

A total of nine patients presented with MGUS, which appeared in six of them before the initiation of the treatment and in three of them while under biotherapy. Therefore, the prevalence of MGUS under biotherapy in our study was 2%, with a mean age of 58.5 years. The incidence was 3/437.

Twenty-seven patients presented with polyclonal hypergammaglobulinemia prior to the initiation of biotherapy, which persisted under treatment. The latter was linked to known cirrhosis in three patients and to chronic sinusitis in one patient. The etiological assessment remained negative for the others. Also noted was the development of polyclonal hypergammaglobulinemia in 21 patients under biotherapy, which enabled the discovery of cirrhosis in 1 of them. A total of 10.5% of the patients presented with polyclonal hypergammaglobulinemia.

The patients were divided into four subgroups according to the results: those presenting with MGUS prior to the treatment, those in whom MGUS developed under biotherapy, those presenting with pre-biotherapy polyclonal hypergammaglobulinemia, and those in whom polyclonal hypergammaglobulinemia developed under biotherapy.

Table 3. Characteristics of patients with MGUS

Patient	Age	Duration of psoriasis	Clinical forms	PR	Prior treatment	Biotherapy	Duration of biotherapy
Female	40	29	Plaque	Yes	PUVA therapy Methotrexate Cyclosporine	Infliximab	42 months
Male	66	27	Plaque	No	UVBTL01 Soriatane	Ustekinumab	7 months
Male	67	10	Pustular Palmoplantar	Yes	Retinoid Cyclosporine	Infliximab Adalimumab	10 months

Measurement units: Age: years; Duration of psoriasis progression: years; Total duration of biotherapy: months.
PR: Psoriatic rheumatism.

Table 4. SPE values of patients with monoclonal gammopathy of undetermined significance (MGUS)

Patient	Gamma globulin type	SPE date	Ig level	Physiological Ig maintained?	Biotherapy	Biotherapy stopped?	Ig level monitored?
1	IgG Lambda	42 months	2.9	Yes	Infliximab	No	No
2	IgG Kappa	7 months	NC	Yes	Ustekinumab	No	No
3	IgG Kappa	10 months	NC	Yes	Infliximab Adalimumab	Yes	Disappearance 1 year after stopping treatment

Ig: Immunoglobulin; SPE: Serum protein electrophoresis.

Table 5. Progression of the immunoglobulin level in patients presenting with gammopathy of undetermined significance (MGUS) prior to biotherapy initiation

Patient	Gamma globulin type	Monitoring date	Ig level	Ig level	Physiological Ig maintained?	Biotherapy
1	IgG kappa	12 months	7.2	8.6	Yes	Ustekinumab
2	IgA kappa	41 months	3.1	2.1	Yes	Infliximab
3	IgG kappa	13 months	3.4	4.3	Yes	Ustekinumab
4	IgG kappa	12 months	NA	NA	Yes	Ustekinumab
5	IgA	60 months	NA	NA	Yes	Efalizumab, Infliximab, Adalimumab
6	IgG kappa	7 months	2.18	1.62	Yes	Infliximab

NA: non assayable; Ig: Immunoglobulin.

Table 6. Variation in SPE values according to demographic and medical history data

	MGUS A	MGUS	Persistence of HG	Development of HG	Normal	p
Number of subjects	6 (1.4%)	3 (0.7%)	27 (6.1%)	21 (4.7%)	386 (87.1%)	
Age:						0.2804
M	59.3	57.7	49.5	52.4	48.2	
SD	17.9	15.3	12.5	14.7	13.4	
Sex:						0.9502
M	4 (66.7%)	2 (66.7%)	17 (63%)	11 (52.4%)	230 (59.6%)	
F	2 (33.3%)	1 (33.3%)	10 (37%)	10 (47.6%)	156 (40.4%)	
Profession:						1
RE	6 (100%)	3 (100%)	26 (96.3%)	20 (95.2%)	359 (93%)	
ARE	0 (0%)	0 (0%)	1 (3.7%)	1 (4.8%)	27 (7%)	
Tobacco	2 (33.3%)	1 (33.3%)	3 (11.1%)	3 (14.3%)	134 (34.7%)	0.0227
Alcohol	2 (33.3%)	2 (66.7%)	6 (22.2%)	5 (23.8%)	44 (11.4%)	0.0063
Arterial hypertension	2 (33.3%)	3 (100%)	8 (29.6%)	6 (28.6%)	96 (24.9%)	0.0747
Dyslipidemia	2 (33.3%)	2 (66.7%)	5 (18.5%)	6 (28.6%)	77 (19.9%)	0.1919
Diabetes	1 (16.7%)	0 (0%)	3 (11.1%)	3 (14.3%)	37 (9.6%)	0.6767
Duration of psoriasis progression:						0.285
M	16.8	18.3	14.2	17.4	19.3	
SD	14.4	10.7	9.6	12.1	12.4	

Measurement units: duration of psoriasis progression: years.
MGUS: Monoclonal gammopathy of undetermined significance; MGUS A: Pre-existing MGUS; MGUS: Discovery of MGUS; HG: Hypergammaglobulinemia; M: Mean; SD: Standard deviation; M: Male; F: Female; ARE: At risk of exposure to toxins; NRE: Not at risk of exposure to toxins.

Statistical analyses among these groups did not indicate any statistically significant link to hypertension, diabetes, or dyslipidemia, nor to the period of psoriasis progression *(table 6)*. There was no link between prior systemic treatments or the type of biotherapy and the development of MGUS or polyclonal hypergammaglobulinemia. However, there was a statistically significant difference between patients presenting with psoriatic rheumatism and MGUS ($p = 0.095$) or polyclonal hypergammaglobulinemia compared to the patients with normal SPE values *(table 7)*.

Discussion

Our study evaluated the link between the use of biotherapies in patients with psoriasis, associated, or not, with psoriatic rheumatism and the development of monoclonal gammopathy, a problem recently debated in the literature [1, 3].
Out of the 443 patients in remission for longer than 6 months who were studied, only 3 developed MGUS at a mean age of 57.7 years. This incidence is low. The first two studies indicated an incidence of 5.9% in 202 patients and 2.66% in 300 patients, respectively [1, 2]. Vilarrasa *et al.* [3] reported an incidence of 0.62%, and Di Lernia *et al.* [4] reported an incidence of 4.44% in 180 patients, lower than that in their control group of psoriasis patients not under biotherapy (5.28% in 492 patients).
The mean development period of MGUS is 19.7 months. It was 12 months in Prignano *et al.* [1], 23 months in Vilarrasa *et al.* [3] and not specified in Di Lernia *et al.* [4]. In all cases, the Igs were IgGs, and the heavy chain was a kappa chain in more than two-thirds of the cases, a ratio similar to that of the general population [5]. None of the MGUS cases

Table 7. Clinical form of psoriasis and SPE abnormalities

Clinical form of psoriasis	MGUS A	MGUS	Persistence of HG	Development of HG	Normal	p
Number of subjects	6 (1.4%)	3 (0.7%)	27 (6.1%)	21 (4.7%)	386 (87.1%)	
Plaque	6 (100%)	2 (66.7%)	24 (88.9%)	20 (95.2%)	338(87.6%)	0.5421
Guttate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	29 (7.5%)	0.4675
Inverse	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)	9 (2.3%)	0.5736
Nail	1 (16.7%)	1 (33.3%)	0 (0%)	2 (9.5%)	19 (4.9%)	0.0544
Scalp	0 (0%)	0 (0%)	1 (3.7%)	3 (14.3%)	20 (5.2%)	0.3971
Pustular	0 (0%)	1 (33.3%)	0 (0%)	2 (9.5%)	10 (2.6%)	0.0568
Palmoplantar	1 (16.7%)	1 (33.3%)	1 (3.7%)	2 (9.5%)	22 (5.7%)	0.1307
Erythrodermic	0 (0%)	0 (0%)	1 (3.7%)	3 (14.3%)	8 (2.1%)	0.0531
Psoriatic rheumatism	1 (16.7%)	2 (66.7%)	12 (44.4%)	10 (47.6%)	94 (24.4%)	0.0095

MGUS: Monoclonal gammopathy of undetermined significance; MGUS A: Pre-existing MGUS; MGUS: Discovery of MGUS; HG: Hypergammaglobulinemia.

presented with risk factors favoring the early development of multiple myeloma according to the criteria of Rajkumar *et al.* (Ig > 1.5g/dL; non-IgG Ig, presence of free light chains) [6].

In the present study, the prevalence of MGUS was 2%, with a mean age of 58.5 years. Kyle *et al.* [7] reported that the frequency of MGUS was 3.2% among 21,463 residents (general population) of Minnesota, USA, in their 50s, and Wadhera and Rajkumar [8] likewise estimated it at 3.2% in patients older than 50 based on an analysis of the literature. Although there was no general population control group in our study, our results do not seem to indicate any increased incidence of MGUS in psoriasis patients relative to the general population.

All of the psoriasis patients with MGUS may have had a contraindication for the administration of biotherapy. Although the good clinical practice recommendations for TNF alpha inhibitors state that it is important to note the history of cancers or pre-cancerous conditions in patients before initiating these biotherapies, they do not formally contraindicate TNF alpha inhibitors [9]. MGUS is considered to be a pre-cancerous condition for which the risk of progression to multiple myeloma is 1% per year [10]. Mielnik *et al.* [11] reported on the case of a patient with a history of ankylosing spondylarthritis presenting with MGUS. Therapy with adalimumab was initiated, which reduced Ig levels and improved the rheumatic symptoms and regression of the inflammatory syndrome, with a 3-year remission. Wendling *et al.* [12] also administered TNF alpha inhibitors to five patients with histories of ankylosing spondylarthritis presenting with MGUS. There was no worsening of the MGUS in these patients after a 5-year remission. In the present study, we were unable to determine the number of psoriasis patients in whom MGUS was discovered in the pre-biotherapy assessment and who were therefore not suited for this treatment. This could have led to an underestimation of the prevalence of MGUS in the psoriatic population prior to and while under treatment.

We also included patients with normal SPE under biotherapy, even if no pre-therapeutic SPE was performed. We thus excluded all patients who may have had MGUS that may have declined under treatment. Although the natural history of MGUS is progression to multiple myeloma, in 2.5% of cases a spontaneous decline occurs upon stopping or starting an immunosuppressant treatment that was initiated in the context of another disease. We therefore do not have remission in the context of this scenario [10] in our study. Even though we likely underestimated the prevalence of MGUS in the psoriatic population under biotherapy in our study, it is still comparable to the general population of the same age group. The use of biotherapies in patients with a history of MGUS is not contraindicated provided that more intense monitoring is performed [9].

Several publications mention the monoclonal Ig level returning to normal after stopping biotherapy treatment [1, 2, 13, 14]. We also noted that one of our patients presented with a non-quantifiable monoclonal gammopathy. However, the monitoring results showed that it had disappeared a year later after stopping the biotherapy. Various hypotheses have been proposed to explain the development of MGUS under biotherapy. The presence of TNF alpha in a multiple myeloma is an indicator of the progression of myeloma. Therefore the TNF alpha inhibitor etanercept was tested in 10 patients with multiple myeloma in a manner similar to other inflammatory conditions, but the treatment was accompanied by a worsening of the multiple myeloma [15]. The physiologically secreted TNF alpha may bind to two receptors, TNF-R1 and TNF-R2, which have a pro-apoptotic and an anti-apoptotic effect, respectively. Etanercept binds mainly to the TNF-R1 receptor via soluble TNF alpha. This may give rise to an imbalance, in turn leading to an increase in the affinity of the TNF alpha for the TNF-R2 receptor. Hence there would be a pro-apoptotic effect with stimulation of cellular synthesis and secretion of monoclonal Ig [16]. Smale *et al.* [14] proposed the same hypothesis to explain an increase in the gamma globulin level under etanercept, which is reversible upon stopping the treatment. Furthermore, in Prignano *et al.* [2], the patients were on efalizumab and the results of that study suggested that the therapeutic Ig accumulated progressively, inducing the secretion of this monoclonal gamma globulin. Hence, stopping the treatment permitted a slow elimination of the Igs and a regression of monoclonal gammopathy. Our results revealed only three cases of MGUS and therefore do not support either hypothesis.

Chronic inflammation may have also played a role in the development of MGUS in these patients with an inflammatory condition, a topic under debate in the literature.

MGUS is reported in connection with many conditions. SPE is in fact a test that is routinely performed in many situations and fortuitous discoveries are possible. There are no recommendations concerning the performance of SPEs in the general population. They are performed in the context of inflammatory, infectious, and auto-immune conditions, which explains the reporting of these numerous associations. Some of these conditions would indeed be triggering factors for the development of MGUS in the context of genetically predisposed susceptibility. However, the exact physiopathology is still poorly understood. Psoriasis has not been reported to be associated with an increased risk of MGUS. In a multicenter cohort study, Bida *et al.* [17] examined the conditions associated with MGUS. Out of more than 17,398 patients, 605 cases of MGUS were found. The two populations with and without MGUS were thus compared. Among them, neither psoriasis nor inflammatory rheumatic conditions were significantly associated with MGUS ($p = 0.67$). That study confirmed a previous study conducted in 2008 [18]. Psoriatic rheumatism, on the other hand, does appear to be associated with SPE abnormalities. This was recently confirmed by a study on 361 patients, although there was no variation between groups that were treated, or were not, by biotherapy [19]. Of the 361 patients, 35 presented with monoclonal gammopathy. Only age ($p = 0.0001$), severity of psoriasis ($p = 0.007$), and duration of psoriasis ($p = 0.02$) appeared to be risk factors for MGUS development. Our numbers are low and do not permit us to draw a conclusion. However, our study does show a slight increase in MGUS and polyclonal hypergammaglobulinemia in patients with psoriatic rheumatism compared to patients with normal SPE values ($p = 0.095$). On the other hand, it was noted that more than 10.1% of the patients had polyclonal hypergammaglobulinemia. The disturbance of the immune system by therapeutic Igs could lead to synthesis of polyclonal gamma globulins. Di Lernia *et al.* [4] put forth the hypothesis that this polyclonal hypergammaglobulinemia secretion is indicative of an underlying immunogenicity developed by the patient in response to biotherapy.

There are no studies on the prevalence of MGUS in psoriasis patients. A previous clinical case report indicated the development of MGUS in patients with histories of psoriasis progressing for more than 15 years, but did not propose a physiopathological explanation [20]. We did not find any significant link between the duration of psoriasis and the development of monoclonal or polyclonal hypergammaglobulinemia in our study.

Since the present study was a retrospective study with a limited number of psoriatic subjects, it has some limitations. However, in the population that we studied, we did not find any evidence of a higher percentage of MGUS development in patients treated with biotherapy.

Conclusion

The incidence of MGUS development in our study is no greater than the presumed 3.2% in the age group of the general population under study. The prevalence of MGUS is likewise comparable. None of our subjects exhibited any severity criteria indicating a risk of progression to multiple myeloma. Attributing the development of MGUS only to the biotherapy does not appear to be justified. A prospective study with greater numbers of patients, including a control group not under biotherapy, would make it possible to define the role of biotherapy in the development of MGUS. Without such a study, our results do not justify retaining the indication of follow-up monitoring for the development of MGUS in patients treated with biotherapy. ■

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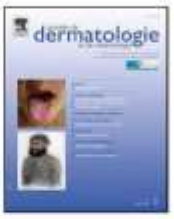

ORIGINAL ARTICLE

Metabolic comorbidities and hypertension in psoriasis patients in France. Comparisons with French national databases☆

suppl. Informations

Comorbidités métaboliques et hypertension artérielle dans le psoriasis en France. Comparaisons aux bases de données nationales

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Summary
Introduction. — Several studies have shown a high prevalence of cardiovascular and metabolic comorbidities in psoriasis. Our study aimed to evaluate the association of psoriasis with key comorbidities such as smoking, obesity, hypertension, dyslipidaemia and diabetes comparatively with French national data.
Material and methods. — This multicentre noninterventional observational study of adults with psoriasis was conducted in 29 dermatology centres in France. A total of 2210 patients were included. The prevalence of comorbidities in psoriatic patients was compared to data from the French national databanks ''ObEpi 2012'' (obesity, hypertension, dyslipidaemia and diabetes) and ''Baromètre Santé 2010'' (smoking).
Results. — We reported a higher prevalence of all metabolic comorbidities and high blood pressure in psoriatic patients. Smoking: 32.5% were active smokers; the age of onset and the prevalence of familial psoriasis were significantly lower in the smoking group but the severity of psoriasis was significantly higher. The frequency of smoking was higher than in the general population, particularly among young female patients. Obesity: 24% of patients with psoriasis were obese. Multivariate analysis showed obesity to be significantly associated with other comorbidities, severity of psoriasis and psoriatic arthritis. The incidence of obesity was higher than in general population, occurring chiefly in subjects aged over 45 years. Hypertension: 26% of patients with psoriasis had hypertension. The age of onset of psoriasis and the prevalence of psoriatic arthritis were significantly higher in the hypertension group, although there was less familial psoriasis. The incidence of hypertension was higher than in general population. Dyslipidaemia: 27.5% of patients with psoriasis had dyslipidaemia. The age of onset in the dyslipidaemia group was higher although there was less familial psoriasis. The incidence of dyslipidaemia was higher than in general population. Diabetes: 11.0% of patients with psoriasis had diabetes. The age of onset of psoriasis was significantly higher in the diabetes group although there was less familial psoriasis. The incidence of diabetes was higher than in general population particularly after the age of 35 years.
Conclusion. — These results confirmed that psoriasis is associated with significant metabolic comorbidities and hypertension compared to the general population in France, with certain epidemiological differences for each.

MOTS CLÉS
Psoriasis ;
Diabète ;
Obésité ;
Hypertension artérielle ;
Dyslipidémie ;
Tabagisme ;
Comorbidités

Résumé
Introduction. — Plusieurs études ont montré une prévalence élevée de comorbidités cardiovasculaires et métaboliques dans le psoriasis. Nous avons évalué l'association du psoriasis aux principales comorbidités comme le tabagisme, l'obésité, l'hypertension, la dyslipidémie et le diabète, par rapport aux données nationales.
Matériel et méthodes. — Cette étude multicentrique observationnelle non interventionnelle d'adultes atteints de psoriasis a été menée dans 29 centres de dermatologie en France ; 2210 patients ont été inclus. La prévalence des comorbidités chez les patients psoriasiques a été comparée aux données nationales françaises : « Baromètre Santé 2010 » pour le tabagisme ; et « ObEpi 2012 » pour l'obésité, l'hypertension, la dyslipidémie et le diabète.

Résultats. — Nous avons constaté une plus grande prévalence de toutes les comorbidités métaboliques et de l'hypertension chez les patients psoriasiques : 1) 32,5 % des patients avaient un tabagisme actif ; l'âge de début du psoriasis et la prévalence du psoriasis familial étaient significativement plus bas dans le groupe des fumeurs, et la sévérité du psoriasis y était significativement plus élevée. La fréquence du tabagisme était plus élevée chez les patients psoriasiques, principalement chez les femmes jeunes ; 2) 24,2 % des patients étaient obèses. L'obésité était associée de manière significative à d'autres comorbidités : la sévérité du psoriasis et le rhumatisme psoriasique en analyse multivariée. La fréquence de l'obésité était plus élevée chez les patients psoriasiques, principalement après 45 ans ; 3) 26,1 % des patients étaient hypertendus. L'âge de début du psoriasis et la prévalence du rhumatisme psoriasique étaient significativement plus élevés dans le groupe hypertendu, alors qu'il y avait moins de psoriasis familial. La fréquence de l'hypertension était plus élevée chez les patients psoriasiques ; 4) 27,5 % des patients avaient une dyslipidémie. L'âge de début du psoriasis était plus élevé dans le groupe « dyslipidémie », alors qu'il y avait moins de psoriasis familial. La fréquence des dyslipidémies était plus élevée chez les patients psoriasiques ; 5) 11,0 % des patients étaient diabétiques. L'âge d'apparition du psoriasis était significativement plus élevé chez les patients diabétiques, alors qu'il y avait moins de psoriasis familial. La fréquence du diabète était plus élevée chez les patients psoriasiques, surtout après 35 ans.
Conclusion. — Ces résultats confirment que, par rapport à la population générale, le psoriasis est associé à des comorbidités métaboliques et à l'hypertension en France ; ils suggèrent l'importance du dermatologue dans la prise en charge de ces comorbidités.

Psoriasis is a chronic inflammatory disease primarily affecting the skin and joints and occurs in 2 to 4% of the French population. Genetic, immunological and environmental factors are all involved in the pathogenesis [1].

For 10 years or so, significant associations have been demonstrated between psoriasis and cardiovascular diseases such as hypertension, coronary disease and major adverse cardiovascular events (MACE), as well as metabolic disorders, mainly obesity, dyslipidaemia, diabetes and ''metabolic syndrome''. A number of extensive studies demonstrate association of addictions such as smoking [2–8]. The direct involvement of psoriasis in the onset of MACE such as myocardial infarction or sudden death syndrome is less clear, pointing to methodological problems in these broad studies [2,3,9–11].

More recently, data in children have confirmed a close and early link between obesity and psoriasis, while the link with other comorbidities in this population (dyslipidaemia, hypertension, diabetes) is currently debated [12–16].

The link between these comorbidities is not clear: could there be a simple epidemiological link? What role does psoriasis play in the onset of these comorbidities? The link is suggested in the hypothesis of ''psoriatic march'' according to which psoriasis plays an aetiological role in the onset of cardiovascular disease. The chronic inflammation induced by the disease is thought to enhance insulin resistance, dysfunction of endothelial cells and atherosclerosis [17–20]. Finally, it has been suggested that through cytokine mechanisms (''lipokine'') mechanisms, obesity may contribute to the onset, and more particularly, the severity of psoriasis [8,21].

Little data is available in France regarding psoriasis and cardiovascular or metabolic comorbidities, and existing data primarily concerns the paediatric population. For instance, it has been shown that obesity and excess weight with abdominal obesity were more frequent in children with psoriasis than in a control group [8], that childhood onset of psoriasis did not predispose subjects to subsequent onset of cardiovascular and metabolic comorbidities [22], and finally that psoriasis occurred more frequently in patients with coronary diseases than in a control group, with coronary disease being more severe in these patients [23].

The aim of the present study was to evaluate the association in France between psoriasis and the principle comorbidities such as tobacco use, obesity, hypertension, dyslipidaemia and diabetes, by comparing the frequencies of these conditions for psoriasis patients with corresponding figures in national databases for the general population.

Methodology

Centres and patients

The methodology of this ''Resopsocar'' study has been described in previous publications [18,20]. It was designed to determine whether childhood-onset psoriasis was associated with cardiovascular and metabolic comorbidities in adulthood [22]. Secondary aims included investigation of psoriasis in relevantly infrequently studied subgroups such as the elderly [24], and the incidence of comorbidities in the French population of psoriasis patients.

This was a cross-sectional, noninterventional, multicentre study of adults presenting psoriasis, conducted between 15 June and 31 October 2011 at 29 French dermatology centres, all belonging to the Resopso Multicentre Studies (GEM) (http://resopso.fr). These 29 centres included university hospitals ($n = 9$), general hospitals ($n = 11$), military hospitals

($n=2$) and private practices ($n=7$). All adult psoriasis patients ($\geq$ 18 years) consulting at the 29 centres over the 4.5 months prior to the study were included consecutively.

Data collection

A data evaluation procedure was implemented using a form specially created for the study. The form comprised 38 items, including data on patients (age, gender), on their psoriasis (age at onset, clinical characteristics, details of any rheumatism, treatment history, familial history—first-degree relatives only), and on risk factors and cardiovascular disease (hypertension, active smoking, body mass index, diabetes and dyslipidaemia). Body mass index (BMI) was determined by dividing subject bodyweight (in kg) by the square of their height (in metres).

Definitions

The diagnosis of psoriasis was made by a dermatologist. Psoriasis was considered severe where a patient required systemic therapy during the course of his or her psoriasis (either before or at inclusion). Definitions of the comorbidities were set out in a previous publication [22]. Obesity was defined as BMI $\geq$ 30 kg/m^2 (moderate: 30—34.9 kg/m^2; severe: 35—39.9 kg/m^2, or morbid: > 40 kg/m^2) [25]. Active smoking at inclusion consisted of patients smoking at least 5 cigarettes/day on the day of inclusion, regardless of the duration of smoking (the number of packets smoked annually was not assessed in this study).

National data

The frequency of cardiovascular and metabolic comorbidities in psoriasis patients was compared with national data: the ''Baromètre Santé 2010'' published by the French National Institute for Health Prevention and Education (INPES) regarding smoking [26], and the ''ObEpi 2012'' study regarding obesity, hypertension, diabetes and dyslipidaemia [27].

The ''Baromètre Santé'' has been published by INPES for the last 20 years. It comprises epidemiological surveys to monitor the key behaviours, attitudes and perceptions associated with risk-taking and the health status of the population resident in Metropolitan France with regard to tobacco and alcohol abuse and consumption of other drugs, vaccination cover, and so on. It is based upon a cross-sectional, telephone survey among a random sample of persons residing in Metropolitan France in ordinary households (with a mobile phone or landline), and aged between 15 and 85 years. The final sample was 27,653 individuals [26].

ObEpi surveys have been conducted every 3 years since 1997. ObEpi 2012 was carried out jointly with Roche and units from Inserm in a sample of 20,000 households representative of the French population of ordinary households contained in the permanent Kantar Health database, and excluding subjects living in institutions, sheltered housing and community residences or having no fixed abode. The panel was constituted using the quota method for households following double stratification by region and habitat. The purpose of this study was to evaluate the frequency of excess weight and obesity (and of associated comorbidities) in France. Out of the 20,000 queries sent out concerning 39,538 individuals aged 15 years and over, 14,705 households returned there questionnaire [27].

Regulatory considerations

Since this was a noninterventional study aimed at collecting totally anonymous data concerning current practice (with no indication of surname/first name or date of birth), no ethics committee declaration was needed (approval was given by a local ethics committee). In all cases, patients were informed about the information being collected. The computerised data form was declared to the French Data Protection Agency (CNIL) on 07/07/2011.

Statistics

Quantitative data were expressed in terms of mean and standard deviation, while qualitative data were expressed as numbers and percentages. Means were compared using a Student's t-test and frequencies were tested using the χ^2 test or Fisher's exact test where necessary. In order to analyse recruitment bias associated with hospital recruitment, analysis was carried out comparing the hospital population included in the study with the population recruited from private practice. Multivariate analysis with logistic regression was conducted to assess the impact of weight, age and gender on the severity of psoriasis and association with psoriatic rheumatism. The comparisons with the national databases were descriptive. The level of statistical significance was taken as $P < 0.05$. Statistical analysis was performed using the SAS v 9.3 software package (SAS Institute Inc., Cary, NC, USA).

Results

During the 4.5 months of the study, 2201 patients were included (56.3% male), with an average age of 48.7 years. The descriptive data for the cohort have already been given. In summary: psoriasis began before 18 years in 24.8% of patients; familial forms were seen in 40.0% of patients (history in at least one first-degree relative); 78.9% of patients had plaque psoriasis, 21.5% had psoriatic rheumatism, and 65.3% were receiving at least one systemic treatment (severe psoriasis) (Table 1) [22].

Smoking

Of the psoriatic patients, 32.5% were active smokers (5 or more cigarettes per day), and 22.2% ($n=486$) had either stopped smoking or smoked fewer than 5 cigarettes per day. Patients in the smoking group were younger and tended to be male. Age at onset of psoriasis and prevalence of familial psoriasis were significantly lower, although the severity of psoriasis was significantly greater (Table 1).

Comparison of the Resopsocar and Baromètre Santé 2010 [26] data showed slightly higher levels of smoking amongst males irrespective of age (0.8 to 6.6%). A similar distinction was seen in female patients, with a more marked difference

Table 1 Psoriasis and comorbidities.

	All patients $n=2201$	Active smoking $n=713$	Hypertension $n=574$	Dyslipidaemia $n=601$	Diabetes $n=241$
Patient's clinical characteristics					
Age (yrs), mean ± SD	48.7 ± 15.5	42.7 ± 13.0$^{<0.0001}$	60.5 ± 12.7$^{<0.0001}$	57.4 ± 12.9$^{<0.0001}$	60.7 ± 11.4$^{<0.0001}$
Males, *n* (%)	1240 (56.3)	422 (59.2)$^{0.04}$	343 (59.8)$^{0.049}$	380 (63.2)$^{<0.0001}$	137 (56.8)
Psoriasis					
Age at onset of psoriasis (yrs), mean ± SD	31.1 ± 17.5	27.3 ± 14.7$^{<0.0001}$	39.8 ± 18.6$^{<0.0001}$	37.9 ± 18.0$^{<0.0001}$	41.3 ± 17.5$^{<0.0001}$
Familial psoriasis, *n* (%)	867 (40.0)	305 (43.6)$^{0.02}$	317 (38.5)$^{0.002}$	210 (35.5)	80 (33.6)$^{0.03}$
Plaque psoriasis, *n* (%)	1633 (78.9)	535 (79.5)	432 (80.9)	441 (78.6)	182 (80.2)
Psoriatic rheumatism, *n* (%)	419 (21.5)	128 (20.1)	132 (26.0)$^{0.003}$	138 (25.5)$^{0.007}$	51 (23.8)
Severe psoriasis, *n* (%)	1437 (65.3)	526 (73.8)$^{0.01}$	410 (71.4)	427 (71.0)	170 (70.5)
Comorbidities					
Obesity, *n* (%)	534 (24.4)	124 (17.6)	255 (44.8)$^{<0.0001}$	223 (37.2)$^{<0.0001}$	123 (51.3)$^{<0.0001}$
Diabetes, *n* (%)	238 (10.9)	42 (5.9)$^{<0.0001}$	150 (26.3)$^{<0.0001}$	157 (20.0)$^{<0.0001}$	—
Dyslipidaemia, *n* (%)	599 (27.5)	159 (22.5)$^{0.0004}$	292 (51.4)$^{<0.0001}$	—	157 (66.5)$^{<0.0001}$
Hypertension, *n* (%)	570 (26.0)	126 (17.7)$^{<0.0001}$	—	292 (49.0)$^{<0.0001}$	150 (62.8)$^{<0.0001}$
Smoking, *n* (%)	712 (32.6)	—	126 (22.3)$^{<0.0001}$	159 (26.8)$^{0.0004}$	42 (17.8)$^{<0.0001}$

Superscript: values of *P* where $P<0.05$, group with comorbidity vs. group without comorbidity. SD: standard deviation.

among younger patients: 4.0 to 13.0% in the 18–54 year age group compared with 1.5% in older patients (Fig. 1).

Obesity

Among the psoriasis patients, 58.1% were overweight (including obese and morbidly obese patients), 24.2% were obese (including morbidly obese patients), and 3.1% were morbidly obese. Univariate analysis showed excess weight to be associated with patients of greater age, male gender, presence of severe and joint psoriasis, and comorbidities (Table 2). Multivariate analysis revealed an association between obesity and severity of psoriasis, psoriatic rheumatism and other comorbidities, i.e. diabetes, dyslipidaemia and hypertension (Table 3).

Comparison of the Resopsocar data and the ObEpi 2012 study data [27] showed that regardless of gender and age, obesity was more common in the psoriasis group. This difference was more pronounced after the age of 45 years (9.0 to 20.8% in men and 12.6 to 17.4% in women) (Fig. 2).

Hypertension

Among the psoriasis patients, 26.1% had hypertension. Patient age, male predominance, age at onset of psoriasis and prevalence of psoriatic rheumatism were all higher in the hypertension group but there were fewer cases of familial psoriasis. The other comorbidities were associated with hypertension, except for smoking (Table 1).

Comparison of the Resopsocar and ObEpi 2012 study data [27] showed a higher incidence of hypertension in the psoriasis group as of 18 years in men and as of 24 years in women. This difference increased markedly as of 45 years in men (≥ 13.7%), and as of 55 years in women (≥ 16.0%) (Fig. 3).

Dyslipidaemia

Among the psoriasis patients, 27.5% were presenting dyslipidaemia. The age was higher and there were more male dyslipidaemia patients. The age of onset of psoriasis was higher and psoriatic rheumatism was more common in the dyslipidaemia group, but there were fewer cases of familial psoriasis. The other comorbidities were associated with dyslipidaemia, except for smoking (Table 1).

Comparison of the Resopsocar and ObEpi 2012 study data [27] showed a higher incidence of dyslipidaemia in the psoriasis group as of the ages of 18 years in men and 35 years in women. This difference in frequency was 15% greater from the age of 35 years onwards in men and 45 years onwards in women (Fig. 4).

Diabetes

11.0% of the psoriasis patients were diabetic. Patient age and age at onset of psoriasis were significantly higher among diabetic patients although there were fewer instances of familial psoriasis. The other comorbidities were associated with diabetes, except for smoking (Table 1).

Table 2 Psoriasis and weight (missing data: $n = 16$).

	Thin $n = 42$	Normal weight $n = 878$	Overweight $n = 743$	Obese [a] $n = 462$	Morbidly obese $n = 69$	P
Patient's clinical characteristics						
Age (yrs), mean ± SD	37.5 ± 17.5	44.9 ± 16.2	50.1 ± 14.2	54.4 ± 13.6	51.4 ± 13.9	< 0.05[b]
Males, *n* (%)	9 (21.4)	436 (49.7)	498 (67.0)	267 (57.8)	25 (36.2)	< 0.0001
Psoriasis						
Age at onset of psoriasis (yrs), mean ± SD	24.2 ± 18.4	28.2 ± 17.1	32.5 ± 17.4	34.8 ± 17.1	32.9 ± 17.4	< 0.05[c]
Familial psoriasis, *n* (%)	16 (38.1)	357 (41.5)	295 (40.5)	167 (36.5)	27 (39.7)	NS
Plaque psoriasis, *n* (%)	26 (66.7)	635 (77.0)	564 (80.6)	355 (82.4)	50 (76.9)	NS
Psoriatic rheumatism, *n* (%)	3 (7.9)	147 (19.0)	141 (21.3)	104 (25.7)	23 (36.5)	0.0004
Severe psoriasis, *n* (%) [c]	23 (54.8)	578 (65.8)	544 (73.2)	343 (74.2)	53 (76.8)	0.003
Comorbidities						
Diabetes, *n* (%)	0 (0)	34 (3.89)	83 (11.2)	105 (22.9)	18 (26.2)	< 0.0001
Dyslipidaemia, *n* (%)	2 (4.8)	146 (16.8)	229 (31.2)	195 (42.5)	27 (40.3)	< 0.0001
Hypertension, *n* (%)	0 (0)	117 (13.4)	199 (26.9)	214 (46.5)	39 (57.4)	< 0.0001
Smoking, *n* (%)	25 (59.5)	347 (39.8)	209 (28.3)	110 (24.1)	14 (20.3)	< 0.0001

Thin is defined as BMI < 18.5 kg/m^2; normal weight as BMI 18.5–24.9 kg/m^2; overweight as BMI 28.5–29.9 kg/m^2; obese as BMI ≥ 30 kg/m^2 (morbidly obese as > 40 kg/m^2) [25]. SD: standard deviation; NS: not significant.
[a] "Obese" includes moderately obese (BMI: 30–34.9 kg/m^2) and severely obese (BMI 35–39.9 kg/m^2).
[b] *P*: 0.05 to 0.01 (thin/normal); *P*: 0.01 to 0.001 (normal/overweight and morbidly obese); *P* < 0.0001 (thin/overweight, obese and morbidly obese; normal/obese; overweight/obese); NS (overweight/morbidly obese; obese/morbidly obese).
[c] *P*: 0.05 to 0.01 (thin/morbidly obese); *P*: 0.01 to 0.001 (thin/overweight; normal/morbidly obese); *P*: 0.001 to 0.0001 (thin/obese); *P* < 0.0001 (normal/overweight and obese; overweight/obese); NS (thin/normal; overweight/morbidly obese; obese/morbidly obese).

Table 3 Impact of age, gender and weight on frequency of comorbidities psoriatic rheumatism and severity of psoriasis. Multivariate analysis (logistical regression).

	P	OR [CI 95%]
Psoriatic rheumatism		
Age	< 0.04	1.008 [1.000–1.015][a]
Gender	0.08	
Weight	< 0.0001	1.262 [1.116–1.427][b]
Severity of psoriasis		
Age	0.01	0.992 [0.986–0.998][a]
Gender	0.005	1.295 [1.080–1.553]
Weight	< 0.0001	1.314 [1.180–1.463][b]

OR: odds ratio; CI: confidence interval.
[a] Risk of developing psoriatic rheumatism increased by 0.8%/year, or decreased by same amount for severity of psoriasis.
[b] Association with psoriatic rheumatism and with severe psoriasis increased respectively by 26.2 and 31.4% on passage from one to another: thin/normal weight/overweight/obese/morbidly obese.

Comparison of the Resopsocar and ObEpi 2012 study data [27] revealed a higher incidence of diabetes in the psoriasis group from the age of 35 years for both sexes with this difference increasing gradually over time (Fig. 5).

Analysis based on recruitment

In order to study the impact of the type of recruitment used (hospital *vs.* private practice), patients recruited using the two inclusion methods were compared (Table 4). There was no difference between the two groups in terms of age, gender, age at onset of psoriasis, familial disease history, incidence of psoriatic rheumatism, obesity, diabetes or dyslipidaemia. In the hospital recruitment group, a higher incidence was noted for plaque psoriasis ($P < 0.0001$), severe psoriasis ($P < 0.0001$), hypertension ($P = 0.02$) and smoking ($P = 0.02$).

Discussion

This multicentre study conducted in 2011 at 29 French centres in 2210 patients presenting cutaneous psoriasis shows an association between psoriasis, comorbidities and risk factors, both cardiovascular (hypertension and smoking) and metabolic (obesity, dyslipidaemia and diabetes). These results confirm the international data for adults, despite differences from one country to another in the epidemiology of these comorbidities (particularly the incidence of obesity) [2–8].

However, our study has certain limitations. The main limitation consists of the comparison with the national

Table 4 Study of populations based on recruitment mode: hospital (22 centres) *vs.* private practice (7 centres).

	Hospital $n=1948$	Private practice $n=253$	P
Patient clinical characteristics			
Age (yrs), mean ± SD	48.7 ± 15.4	48.3 ± 15.9	NS
Males, *n* (%)	1104 (56.7)	136 (53.8)	NS
Psoriasis			
Age at onset of psoriasis (yrs), mean ± SD	31.1 ± 17.5	31.1 ± 17.7	NS
Familial psoriasis, *n* (%)	765 (39.9)	102 (41.3)	NS
Plaques psoriasis, *n* (%)	1484 (80.5)	149 (66.5)	< 0.0001
Psoriatic rheumatism, *n* (%)	370 (21.2)	49 (24.7)	NS
Severe psoriasis, *n* (%)	1300 (66.7)	137 (54.2)	< 0.0001
Comorbidities			
Obesity, *n* (%)	468 (24.0)	592 (23.3)	NS
Diabetes, *n* (%)	218 (11.2)	20 (7.9)	NS
Dyslipidaemia, *n* (%)	530 (27.4)	69 (27.9)	NS
Hypertension, *n* (%)	520 (26.8)	50 (19.9)	0.02
Smoking, *n* (%)	647 (33.4)	65 (26.0)	0.02

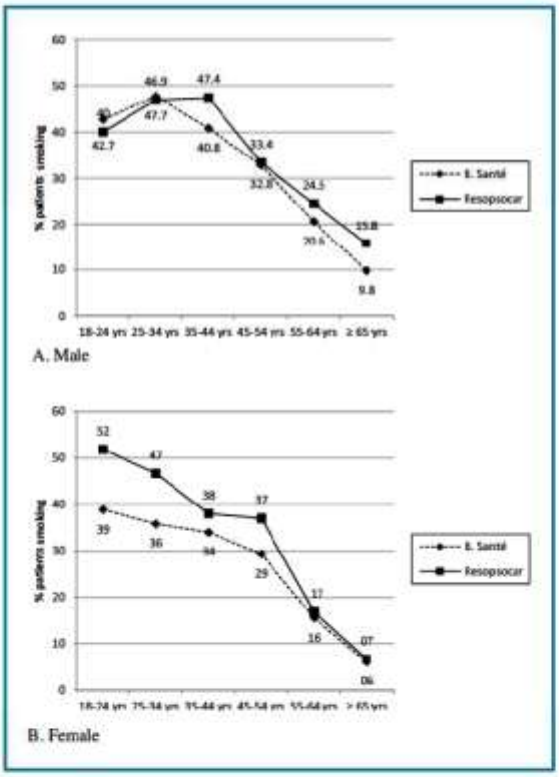

Figure 1. Frequency of smoking among patients by age and gender. Comparisons between patients presenting psoriasis (Resopsocar) and the general French population (Baromètre Santé 2010) [26].

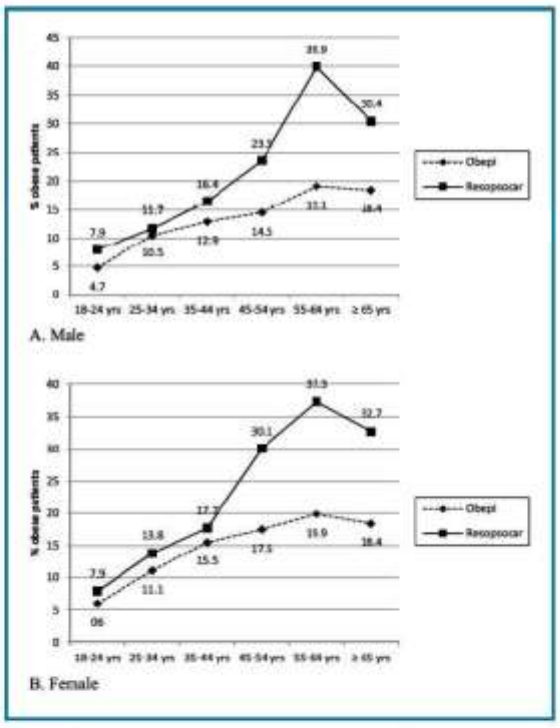

Figure 2. Frequency of obesity (BMI ≥ 30 kg/m^2) among patients by age and gender. Comparisons between patients presenting psoriasis (Resopsocar) and the general French population (ObEpi 2012) [27].

Baromètre Santé 2010 data and ObEpi 2012 study data, with widely different methodologies being used in the three cases [26,27]. First, the definitions of comorbidities in each case were not strictly identical, particularly as regards smoking: in the Baromètre santé 2010 study, this referred to daily smokers (i.e. subjects reporting that they smoked at least one cigarette, one cigar, one cigarillo or one pipe per day) irrespective of the number of cigarettes actually smoked, whereas we adopted a limit of 5 cigarettes per day in the Resopsocar study. Consequently, we probably underreported

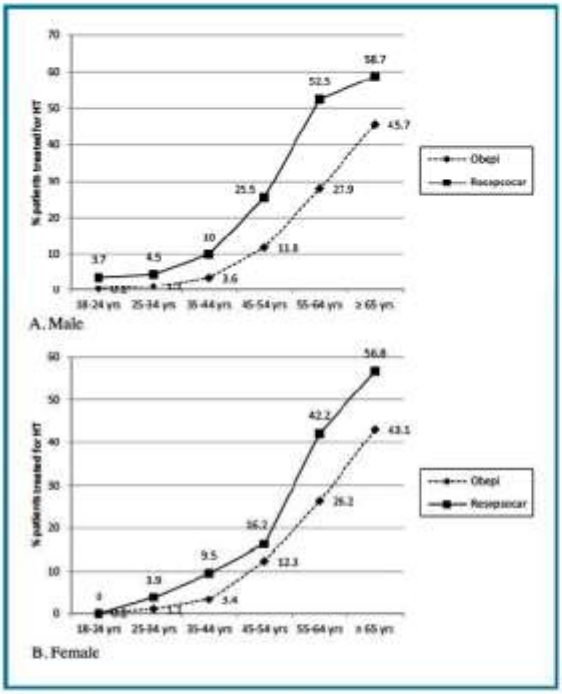

Figure 3. Frequency of hypertension among patients by age and gender. Comparisons between patients presenting psoriasis (Resopsocar) and the general French population (ObEpi 2012 data) [27].

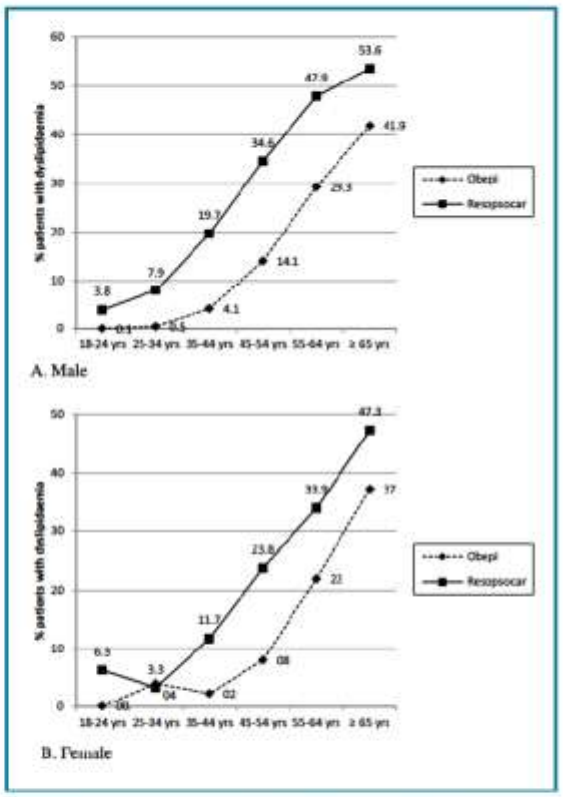

Figure 4. Frequency of dyslipidaemia among patients by age and gender. Comparisons between patients presenting psoriasis (Resopsocar) and the general French population (ObEpi 2012) [27].

the number of ''daily smokers'' in relation to the Baromètre Santé 2010 data [26]. The definition of obesity was the same in the two studies, with the international definition recognised in France being used [25]. Regarding hypertension, diabetes and dyslipidaemia, diagnosis was based on the notion of ongoing treatment in the ObEpi study [27], whereas in the Resopsocar study, both laboratory and clinical data were also used.

Although the national studies are based upon studies with ''robust'' quotas in terms of representativeness of the general population [22,23], our patients were included consecutively in centres specialising in psoriasis, with the possibility of selection bias regarding patients presenting comorbidities and who might thus be unrepresentative of the general population of psoriasis patients. The hospital effect involving recruitment of more ''difficult'' patients could also have resulted in a major bias with regard to the incidence of comorbidities and was thus analysed. Comparison of hospital recruitment and recruitment by private practitioners, resulting in a population closer to the general population, revealed no differences in terms of age, gender, incidence of psoriatic rheumatism, obesity, diabetes or dyslipidaemia. In the hospital cohort, hypertension and smoking were slightly less common, as were severe forms of psoriasis. The ''hospital recruitment'' effect may thus have introduced some statistical bias with regard to these two diseases.

The method of diagnosis of the comorbidities also differed: while comorbidities were declared by patients (surveys by mail and telephone) in the national studies, medical diagnosis was used in the Resopocar study. There thus exists a bias of potential underreporting in the national studies due to the diagnostic method used.

The criterion of severity used in this study is open to discussion. It is important in assessing the relationship with obesity. In our study, we opted for a definition of disease severity based on use of conventional systemic therapy or biotherapy. The scores generally used are the Psoriasis Area and Severity Index (PASI), the Dermatology Quality of Life Index (DLQI), and the area of skin affected [28]. While these scores are useful for ad hoc assessment of the disease or therapeutic monitoring (e.g. therapeutic trials), they do not adequately reflect the long-term severity of the disease and are suitable as clinical scoring systems only for plaque psoriasis (thus excluding 20% of our patients). Systemic therapy is only used in moderate-to-severe psoriasis regardless of clinical type, and in normal practice, this seemed to us to reflect severity over the long term. Since the aim of our study was to compare the severity of psoriasis with the incidence of chronic diseases (comorbidities), this criterion of ''systemic therapy'', which reflects the chronic severity of psoriasis, seemed to us to be more suitable.

Finally, these studies were not conducted simultaneously, and it has been shown that the frequency of comorbidities

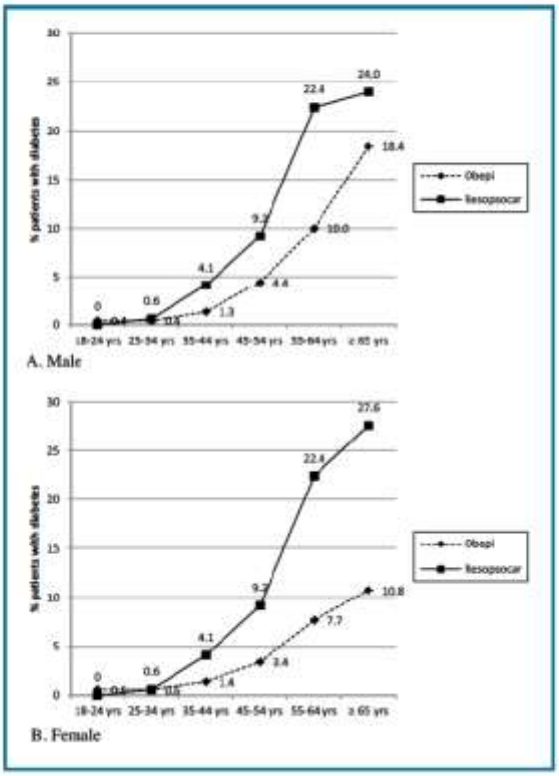

Figure 5. Frequency of diabetes among patients by age and gender. Comparisons between patients presenting psoriasis (Resopsocar) and the general French population (ObEpi 2012) [27].

varies with time: for example, in France, tobacco smoking tends to decrease over time while obesity tends to increase. However, the variations noted over time in the Baromètres santé data and the ObEpi studies were extremely gradual. Thus, regarding smoking, for the entire population aged 15 to 75 years, after a significant decrease between 2000 (30.0%) and 2005 (27.0%), the number of daily smokers rose by 2% between 2005 and 2010 to 29.1% ($P<0.001$) [26]. The prevalence of obesity between 2009 and 2012 increased from 14.5 to 15% (+3.5%) between the ObEpi studies in 2009 and 2012 [27]. These minor variations over time cannot account for the differences observed in our study, conducted one year after Baromètre Santé 2010 and one year before the ObEpi 2012 study.

The Resopsocar study was not designed to study the frequency of these comorbidities or to compare them to the national data (a secondary study aim). However, the tendencies noted in our study argued in favour of an excessive number of cardiovascular and metabolic comorbidities in the psoriatic population, to a greater extent in young women regarding smoking and in patients of both sexes after the age of 45–50 years. For all comorbidities, patient age as well as the age of onset of psoriasis appeared higher, except for smoking. One of our recent publications dealing with psoriasis in elderly subjects effectively showed a significantly higher incidence of comorbidities in the group of subjects aged over 70 years, except for smoking [24]. In another study conducted in Malaysia, comorbidities such as hypertension, diabetes, dyslipidaemia and obesity were more frequent in patients presenting late-onset psoriasis. Furthermore, there were significantly fewer instances of familial psoriasis among patients presenting hypertension, dyslipidaemia or diabetes [29].

Smoking was seen more frequently in psoriasis patients, particularly young women, and particular vigilance is thus called for in this specific age group. Tobacco consumption in male patients was globally equivalent to that of the general population and smoking is comparable between male and female psoriasis patients. Previous studies have emphasised the role of smoking in the pathogenesis and incidence of psoriasis [30,31].

The association between obesity and psoriasis appears to have been confirmed in France, particularly after 45 years, and some studies have advanced the hypothesis that obesity constitutes an acquired risk factor predisposing towards the development of psoriasis in old age [32]. Further, associations between obesity and psoriatic rheumatism and between obesity and severity of psoriasis emerged from the multivariate analysis performed in this study, as suggested by other studies in both children and adults [8,11,12,33–36].

The familial form of psoriasis was significantly noncorrelated with the comorbidities. This could suggest a less important role of these comorbidities in the forms of psoriasis involving a greater genetic component, and conversely, a direct impact of these common entities on sporadic forms of psoriasis.

The marked prevalence of cardiovascular and metabolic comorbidities in psoriasis patients suggests that dermatologists should play a key role in the management of these comorbidities. While dermatologists are not qualified to treat all of these comorbidities, they have an important role to play in the detection thereof and in encouraging patients to seek suitable treatment [37–39]. This is all the more important since treatments for psoriasis tend to augment the frequency and severity of these comorbidities (e.g. acitretin and dyslipidaemia, cyclosporine and hypertension, anti-TNF alpha and weight gain) [40], while weight has a direct effect on the prescribed dose, particularly for biotherapy [41–43], and also given that recent studies suggest that reducing patient weight increases the efficacy of their psoriasis treatment [44].

Conclusion

This study confirms that in France, psoriasis is associated with cardiovascular and metabolic comorbidities such as smoking, obesity, hypertension, dyslipidaemia and diabetes. These results underline the importance for dermatologists of paying particularly close attention to the detection and treatment of comorbidities in psoriasis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.annder.2015.06.024.

Disclosure of interest

M.-L. Sigal has received speaker fees from Janssen-Cilag.

M. Lahfa works as a consultant for Janssen-Cilag, Novartis, Abbvie, MSD and Pfizer, and has received speaker fees from Abbvie, Janssen-Cilag, Novartis, Pfizer, Leo pharma, Galderma, Pierre Fabre Dermatologie and MSD and works as an investigator for Leo, Janssen-Cilag, Novartis, Abbvie, Celgène and Pierre Fabre.

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E. Bégon has received speaker fees from Abbvie, Janssen-Cilag, Leo, MSD and Pfizer.

P. Bravard has received speaker fees from Abbvie, Janssen-Cilag, Pfizer and Schering-Plough and works as an investigator for Abbvie.

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C. Phan, M. Bastien-Jacquin, A. Beauchet, P. Pfister, E. Sauques, J. De Quatrebarbes, P. Tousssaint, M. Alexandre and T. Boyer declare that they have no competing interest.

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ORIGINAL ARTICLE

New-onset vitiligo and progression of pre-existing vitiligo during treatment with biological agents in chronic inflammatory diseases

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Abstract

Background The development of vitiligo during treatment with biological agents is an unusual event and only a few isolated cases have been reported.

Objectives To describe the clinical characteristics and evolution of patients developing new-onset vitiligo following initiation of a biological agent for chronic inflammatory disease; and also to report the clinical course of pre-existing vitiligo under biological therapy.

Methods This nationwide multicentre, retrospective study, carried out between July 2013 and January 2015, describes the characteristics of a large series of 18 patients (psoriasis $N = 8$, inflammatory rheumatic diseases $N = 8$, ulcerative colitis $N = 1$, uveitis $N = 1$) who developed new-onset vitiligo while receiving a biological agent.

Results TNFα inhibitors were the most common biological agent involved (13/18) while anti-IL-12/23 and anti-IL-17 agents or abatacept were less common (4/18 and 1/18 respectively). Mean duration of biological agent exposure before vitiligo onset was 13.9 ± 16.5 months. Outcome was favourable for most patients (15/17) while maintaining the biological agent. Data were also collected for 18 patients (psoriasis $N = 5$, inflammatory rheumatic diseases $N = 10$, inflammatory bowel diseases $N = 2$, SAPHO $N = 1$) who had pre-existing vitiligo when treatment with a biological agent started (TNFα inhibitors $N = 15$, ustekinumab $N = 1$, rituximab $N = 1$, tocilizumab $N = 1$). Vitiligo progressed in seven patients and was stable or improved in eight cases.

Conclusion Vitiligo may thus emerge and/or progress during treatment with various biological agents, mainly TNFα inhibitors and could be a new paradoxical skin reaction. *De novo* vitiligo displays a favourable outcome when maintaining the biological agent, whereas the prognosis seems worse in cases of pre-existing vitiligo.

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Conflicts of interest

L. Méry-Bossard has received speaker honoraria from AbbVie and Pfizer. F. Maccari is a consultant for Janssen-Cilag and has received speaker honoraria from AbbVie and Janssen-Cilag. J.L. Perrot is a consultant for AbbVie, Janssen-Cilag, MSD and Novartis. Z. Reguiai is a consultant for Janssen-Cilag and Pfizer; has been an investigator for AbbVie, Novartis, Pfizer; has received speaker honoraria from AbbVie, Janssen-Cilag and Pfizer. M.L. Sigal has received speaker honoraria from Janssen-Cilag. T. Boyé has received speaker honoraria from

AbbVie, Novartis and Pfizer. A. Grasland has received speaker honoraria from AbbVie, BMS, Pfizer, Roche. D. Jullien is an advisory board member and received speaker honoraria from AbbVie, Janssen-Cilag, Lilly, Novartis and Pfizer; and is investigator for Amgen. K. Bagny, G. Chaby, A. Khemis, H. Marotte, M.Avenel-Audran, J.Gillard ans E. Toussirot declare no conflict of interest in this article.

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None.

Introduction

Tumour necrosis factor alpha (TNFα) inhibitors have been used for many years in the treatment of different chronic inflammatory diseases including inflammatory bowel diseases, inflammatory rheumatic diseases and psoriasis. Anti-lymphocyte B (rituximab) and costimulatory blockers (abatacept, a CTLA-4 fusion protein) are also available to treat rheumatoid arthritis. More recently, biological therapies targeting the Th17/IL-12/23 pathway have been developed and ustekinumab, an anti-p40 IL-12/23 product, is currently on the market for the treatment of psoriasis and psoriatic arthritis. All these different biological agents have been associated with various adverse events affecting the skin, with a frequency ranging from 10% to 60%.[1–3] In a 5-year prospective analysis of patients with chronic inflammatory arthritis, the main risk factors for cutaneous events under TNFα inhibitors were identified as advanced age, female sex, diagnosis of rheumatoid arthritis, disease activity and the use of infliximab.[2] Psoriasis is among the most widely reported cutaneous side-effect of anti-TNFα therapy and is considered to occur as a paradoxical skin reaction.[4]

Vitiligo is a common depigmenting disorder affecting around 0.5% of the world population.[5] The development of new-onset vitiligo upon initiation of a biological agent is an unusual event and only a few isolated cases have been reported.[1,6–12] In parallel, biological agents given for an autoimmune disease may potentially influence the outcome of pre-existing vitiligo. We thus conducted this study to describe the clinical characteristics and evolution of patients developing new-onset vitiligo following initiation of a biological agent for chronic inflammatory disease. We also reported the clinical course of pre-existing vitiligo under biological therapy.

Patients and methods

Study design

This study was carried out between July 2013 and January 2015. This was an observational retrospective, nationwide multicenter study. A call for new cases of vitiligo, following initiation of biological treatment (anti-TNFα [infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept], anti-IL-6 [tocilizumab], anti-CD20 [rituximab], anti-IL-1 [anakinra], anti-IL-12/23 [ustekinumab] and anti-IL17 [secukinumab]) was sent to the members of the French specialist networks « *Resopso* » (dermatologists), the French Society of Dermatology (SFD) and '*Club Rhumatismes et Inflammation*' (CRI) (rheumatologists and specialists in internal medicine), using a standardized questionnaire available on specific website. Patients with pre-existing vitiligo and receiving a biological agent for another chronic inflammatory disease were also recorded as a comparative group. The diagnosis of vitiligo had to be confirmed by a dermatologist. For pre-existing vitiligo, the changes in skin pigmentation also had to be evaluated by a dermatologist. Demographic characteristics (age, sex) and clinical data (medical history, underlying inflammatory disease, biological agent, time frame between starting treatment with a biological agent and onset/modification of vitiligo), type (localized, generalized, segmental) and site(s) of vitiligo, outcome of vitiligo and prescribed treatments were recorded for all patients.

Table 1 Clinical characteristics and outcome of patients developing *de novo* vitiligo and patients with pre-existing vitiligo while receiving a biological agent for a chronic inflammatory disease

	***De novo* vitiligo *N* = 18**	**Pre-existing vitiligo *N* = 18**
Sex (M/F), *n*	11/7	9/9
Age (years), mean ± SD [median]	42.8 ± 12.8 [43.5]	53.0 ± 14.7 [56.5]
Underlying inflammatory disease, *n*		
Psoriasis	8	5
Psoriatic arthritis	/	3
Rheumatoid arthritis	4	6
Ankylosing spondylitis	4	1
Ulcerative colitis	1	1
Crohn's disease	/	1
Pan uveitis	1	/
SAPHO	/	1
Previous medical history, *n*		
Lupus	1	1
Diabetes	2	1
Crohn's disease	1	/
Thyroiditis	/	4
Familial history of vitiligo, *n*	/	1

Table 2 Vitiligo history

	De novo vitiligo *N* = 18	Pre-existing vitiligo *N* = 18
Biological agent, *n*		
Adalimumab	8	7
Infliximab	3	4
Etanercept	/	4
Certolizumab	2	/
Ustekinumab	3	1
Rituximab	/	1
Tocilizumab	/	1
Abatacept	1	/
Secukinumab	1	/
Time frame between initiation of biological agent and vitiligo appearance/modification (months), mean ± SD [median]	13.9 ± 16.5 [10]	13.8 ± 22.9 [14.5]
Site of vitiligo (*n* = 15), *n*	(known for 15 cases)	(known for 14 cases)
Disseminanted	/	2
Trunk and limbs	10	10
Face/head	3	2
Peliosis	1	/
Leucotrichia	1	/
Maintenance of the biological agent (yes), *n* (%)	12 (66.7)	17 (94.4)
Outcome, *n* (%)*		
Progression	2 (11.8)	7 (43.7)
Stable	9 (52.9)	8 (50.0)
Repigmentation	6 (35.3)	1 (6.2)

*Lacking data: one in the '*de novo*' group, two in the 'pre-existing' group.

Results

First group: new-onset vitiligo

Eighteen new cases of vitiligo were reported by 12 French hospitals. Eleven patients (61%) were male and the mean age was 42.8 ± 12.8 years (median: 43.5, range: 17–69). Non-segmental vitiligo was diagnosed in 17 patients and leucotrichia in one. No patient had any previous personal/family history of depigmenting or thyroid disease but one had developed paradoxical psoriasis during a previous course of biological treatment. Four others had concomitant chronic inflammatory disease (Table 1). The underlying inflammatory diseases requiring the biological agent were psoriasis ($n = 8$), rheumatoid arthritis ($n = 4$), ankylosing spondylitis ($n = 4$), ulcerative colitis ($n = 1$) and panuveitis ($n = 1$). Adalimumab was the most common biological agent involved ($N = 8$), followed by infliximab ($N = 3$) and ustekinumab ($N = 3$), while abatacept ($N = 1$) and secukinumab ($N = 1$) were less commonly used (Table 2). The biological agent was given as a first-line treatment to twelve patients. Four of them had concomitant therapy with leflunomide ($N = 1$), methotrexate ($N = 1$) or oral corticosteroids ($N = 2$). Mean time between biological agent initiation and vitiligo onset was 13.9 ± 16.5 months (median: 10, range 1–72). Vitiligo was localized, and usually affected the trunk, limbs or face (Figs 1–3). In 12/18 (66.6%) patients, the biological agent was continued without worsening of vitiligo. Fifteen out of 18 patients (83.3%), experienced stabilization or partial repigmentation, while the skin disease progressed in two cases (outcome was unknown in one case). Skin depigmentation was treated by topical application in six cases (dermocorticosteroids $N = 4$, tacrolimus $N = 2$). Biological agent was switched in three cases because of uncontrolled underlying inflammatory disease (two from adalimumab to etanercept and one from infliximab to ustekinumab), without progression of vitiligo. In three cases, the biological agent (infliximab $N = 2$, abatacept $N = 1$) was permanently

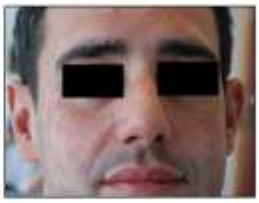

Figure 1 Vitiligo onset 1 month after adalimumab for psoriasis (first-line biotherapy).

Figure 2 Repigmentation after switch from adalimumab to ustekinumab.

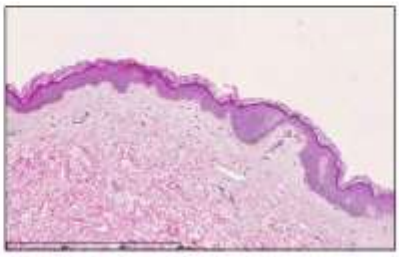

Figure 3 Skin biopsy of the same patient: hypopigmentation of basal lining cells and decreased number of melanocytes.

stopped. Skin depigmentation remained stable in two of these patients and improved in one during follow-up.

Second group: pre-existing vitiligo

Eighteen patients had pre-existing non-segmental and stable vitiligo at the time of starting treatment with a biological agent. They were declared by 12 different centres. Nine patients (50%) were male and the mean age was 53.0 ± 14.7 (median: 56.5, range: 20-72). Four patients had thyroid disease and one had a family history of vitiligo (Table 1). Mean duration of vitiligo before starting treatment with a biological agent was 257.0 ± 170.2 months (median: 238, range: 7–604 months). The inflammatory diseases requiring a biological agent were: psoriasis ($N = 5$), rheumatoid arthritis ($N = 6$), psoriatic arthritis ($N = 3$), ankylosing spondylitis ($N = 1$), SAPHO syndrome ($N = 1$), ulcerative colitis ($N = 1$) and Crohn's disease ($N = 1$). For 11 of the patients, this was the first time a biological agent had been used. The biological agents used were TNFα inhibitors in 15 cases (adalimumab $N = 7$; infliximab $N = 4$; etanercept $N = 4$), while the others received ustekinumab ($N = 1$), rituximab ($N = 1$) or tocilizumab ($N = 1$) (Table 2). The main sites of vitiligo were the trunk and limbs (71.4%). After initiating the biological agent, progression of vitiligo was observed in seven cases, stability in eight and one case of partial repigmentation was observed (outcome was unknown in two cases). Concomitant therapies were known for ten patients (unknown for eight patients): methotrexate was associated with the biological agent in three patients in the stable group and one in the worsening group, the others having no associated therapy. Vitiligo progression was observed in patients under adalimumab ($N = 4$), infliximab ($N = 2$) and etanercept ($N = 1$). The mean delay between the start of treatment with the biological agent and changes in skin pigmentation was 13.8 ± 22.9 months (median:14.5). The treatment was maintained in 17 cases and was stopped for one patient. Skin depigmentation was treated by dermocorticoids in one case, and by topical tacrolimus in two cases. No patient was switched to another biological agent.

The mean follow-up time after vitiligo appeared (first group) or progressed/improved/stabilized (second group) was 32 ± 14 months. This was similar in the two groups.

Discussion

There have only been a few studies reporting a link between the use of a biological agent in inflammatory diseases and the development of *de novo* vitiligo and/or progression of pre-existing vitiligo.[1,6–12] We describe here the largest series of 18 patients with vitiligo that appeared during biological therapy (first group) and in parallel, a group of 18 patients who had pre-existing vitiligo at the time of starting a biological agent, with depigmention that progressed in roughly half of them (second group).

The patients in the first group were predominantly male, but they were older than those with common vitiligo.[13] In this group, a small number had an associated autoimmune condition while thyroid disease was more common in the second group. New-onset vitiligo under a biological agent is considered to be a rare event estimated to occur in 1/5437 patients in one study.[14] Most reports of *de novo* vitiligo under a biological agent have been described as isolated cases associated with the use of infliximab[1,6–9] or adalimumab.[11,12] There have been two cases in which the type of biological agent was not specified.[10] Skin depigmentation appeared within 6–8 months after starting the biological agent. This is shorter than in our first group of patients. New-onset vitiligo in our series was associated with the use of different biological agents but TNFα inhibitors were over-represented (72.2%), only with monoclonal antibody (no cases were observed with etanercept), while anti-IL-12/23 or anti-IL-17 agents were less well represented (22.2%). However, TNFα inhibitors are currently the most widely prescribed biological agent in different inflammatory diseases and this could have influenced the results. Most of our patients ($N = 12$) continued their biological agent and their skin disease improved or stabilized, indicating that *de novo* vitiligo had a favourable outcome and prognosis. However, the skin lesions were treated by topical agents in six cases, which may have influenced this outcome.

Pre-existing vitiligo may also change under exposure to a biological agent. Indeed, in our second group, vitiligo worsened in half of the patients, while the others experienced stability or even improvement. Associated inflammatory conditions and a family history of depigmenting disorder are more often observed in this group compared to the first one. Again, in the second group, TNFα inhibitors were mainly associated with progression of vitiligo with a predominance of monoclonal antibodies ($N = 6$ vs. only one case under etanercept).

The mechanism by which a biological agent may be associated with the development/progression of vitiligo is unknown. TNFα is a pro-inflammatory cytokine that plays a central role in the pathogenesis of vitiligo.[13,14] Indeed, abnormal expression of TNFα has been described in lesional vitiligo skin, with a level of expression related to disease severity.[15] TNFα inhibits melanocyte differentiation from stem cells and melanocyte function.[16] TNFα also destroys melanocytes through induction of apoptosis.[17] Conversely, TNFα can activate and induce proliferation of T regulatory cells (Treg) and T reg abundance is markedly reduced in the skin of vitiligo patients.[18] Therefore, blocking the TNFα pathway may be useful in lesional vitiligo skin.[19] However, results on the effects of TNFα inhibitors in patients with vitiligo are not convincing. Indeed, small series of patients receiving infliximab, adalimumab or etanercept showed no or mild improvement of depigmenting lesions.[20–22] On the contrary, our series and previous reported cases illustrated well that TNFα inhibitors and other biological agents may be associated with the emergence/progression of vitiligo. The underlying mechanisms for explaining this unexpected reaction are that the biological agent may lead to local changes

to the cytokine balance and/or activation of alternative pathways such as type I interferon, as is described for psoriatic-induced lesions.[4] Inhibiting TNFα can also be associated with a decrease in T reg production and activation and less T reg skin homing that allow T-cell autoreactivity against melanocytes.[18,23] IFN γ is another cytokine that plays a central role in vitiligo by suppressing T reg function and inducing melanocyte apoptosis.[24,25] PBMCs from patients with vitiligo display high expression of t-bet and IFNγ.[26] A dual role for TNFα inhibitors on Th1/Th2 cytokine balance has been reported in spondyloarthritis, reducing (infliximab) or enhancing (etanercept) IFNγ production.[27,28] Tofacitinib, an anti JAK1/2 synthetic drug used in rheumatoid arthritis, may improve vitiligo.[29] IFNγ signal transduction occurs through JAK1/2, and IFNγ induced the expression of CXCL10 chemokine in keratinocytes that can interact with CXCR3 on autoreactive CD8+ T cells. The IFNγ/JAK 1/3/chemokine CXCL10-CRCX3 pathway seems to be a key determinant in vitiligo development. NALP1 genetic variants have been linked to vitiligo and thus, another hypothesis is that the biological agent may interfere with innate immunity in selected and genetically predisposed patients.[30, 31]

Co-occurrence of vitiligo with inflammatory diseases is well described[5,13,32,33] and thus, the development/worsening of skin depigmentation may be coincidental and related to the underlying disease. However, predisposing factors such as family history were poorly represented in our two series. Three patients in the first group had to switch biologic because of the uncontrolled inflammatory disease. Thus, in these three cases, we may consider that the underlying uncontrolled disease could promote vitiligo onset.

Whether or not the biological agent should be discontinued at vitiligo onset and/or worsening is a relevant issue. Most of our patients with *de novo* vitiligo had a favourable outcome while continuing to take the same biological agent. However, some of the patients had concomitant topical treatment. Considering our series of vitiligo onset, we can thus recommend continuing the biological agent. A worse outcome was observed in 44% of the patients with pre-existing vitiligo. It is known that vitiligo is associated with psychological consequences and has an impact on self- esteem. Thus, the benefits of the biological agents for the underlying chronic inflammatory disease must be balanced with the consequences of skin depigmentation in terms of quality of life. In this sense, assessing the activity of the inflammatory disease and using a quality of life questionnaire may be helpful.

It has recently been suggested that TNFα inhibitors have different effects depending on the subgroup of vitiligo.[14] Indeed, stabilization of disease or repigmentation may be obtained with TNFα inhibitors in patients with progressive vitiligo. However, worsening can occur if the skin disease is stable. This is consistent with the outcomes observed in our second group of patients who experienced different outcomes. However, the disease activity and potential of vitiligo to progress has not been specifically evaluated in our series using adapted outcome measures.

Our study had limitations; it was retrospective and was small in size. However, it is the largest series reported to date that described clinical situations in real practice, providing informative data for clinicians.

Conclusion

New-onset vitiligo or progression of pre-existing vitiligo is a rare but not exceptional event that can occur with TNFα inhibitors and other biological agents. Whether this could represent a new paradoxical skin reaction or not remains an open question. *De novo* vitiligo displays a favourable outcome when the biological agent was maintained, while the prognosis seems worse in cases of pre-existing vitiligo which progressed. Thus, clinicians must be aware of this unexpected adverse event in skin, and should closely observe and evaluate their patients' skin when introducing a biological agent, especially in cases of pre-existing depigmentation.

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LETTER TO THE EDITOR

Anti-PD1-induced psoriasis: a study of 21 patients

Nivolumab (Opdivo®), pembrolizumab (Keytruda®), atezolizumab and pidilizumab are anti-PD1 monoclonal antibodies. Nivolumab is licensed in advanced melanoma and second-line therapy of advanced or metastatic non-small cell lung cancer. When activated, the programmed cell death (PD)-1 is implicated in the inhibition of the immune system. Anti-PD1 removes this inhibition and allows the immune system to control tumour cell progression.[1–4] Immune-mediated toxicity of this treatment have been reported, either organ-specific toxicities – i.e. pneumonia, colitis, hepatitis, hypophysitis and thyroiditis – or skin toxicities – i.e. vitiligo, photosensitivity, lichenoid eruption. Recently, cases of anti-PD1-induced psoriasis have been reported.[5–8] The aim of this study was to describe the

Table 1 Cases of anti-PD1-induced psoriasis

Case	Sex, age (y)	History of psoriasis		Cancer		Anti-PD1-induced psoriasis		Evolution		
		Yes/ No	Clinical type	Cancer type	Anti-PD1	Nb infusions/ delay (d) [a]	Clinical type	Anti-PD1	Treatment	Evolution
1	M, 67.0	Yes	Sebopsoriasis	Lung cancer	Nivolumab	2/16	Plaque/PuPPP	Continued	Local	Improved, and 2nd flare after 6th injection
2	M, 59.2	Yes	Plaque	Melanoma	Nivolumab	3/31	Plaque/PPP	Continued	Local	Improved
3	M, 81.0	Yes	Plaque	Lung cancer	Nivolumab	2/16	Plaque/guttate	Continued	Local	Improved
4	M, 58.9	Yes	Guttate	Melanoma	Nivolumab	2/29	Plaque/guttate	Continued	Local	Improved
5	M, 67.5	Yes	Plaque	Melanoma	Nivolumab	4/50	Plaque/guttate	Continued	Local + acitretin	Improved
6	M, 61.8	Yes	Scalp	Lung cancer	Nivolumab	2/28	Plaque	Stopped	Local	Improved
7	F, 59.3	Yes	Scalp	Lung cancer	Nivolumab	3/36	Plaque / PPP	Continued	Local	Improved
8	M, 81.5	Yes	Guttate	Lung cancer	Nivolumab	6/98	Plaque/guttate	Continued	Local + acitretin	Improved
9	M, 65.9	Yes	Guttate	Lung cancer	Nivolumab	2/19	Plaque	Stopped	Local + acitretin	Improved
10[b]	*M, 87*	Yes	*Plaque*	*Melanoma*	*Nivolumab*	*2/21*	*Plaque/guttate*	*Stopped*	*General CS*	*Improved*
11[b]	*M, 65*	Yes	*Plaque*	*Melanoma*	*Nivolumab*	*1/21*	*Plaque*	*Continued*	*Local + acitretin*	*Improved*
12	M, 35.2	Yes	Plaque	Melanoma	Pembrolizumab	1/31	Plaque	Continued	Local	Worsened[b]
13	F, 50.5	Yes	Scalp	Melanoma	Pembrolizumab	2/48	Plaque/PPP	Continued	Local	Improved
14[4]	*M, 67*	Yes	*Plaque*	*Lung cancer*	*Pembrolizumab*	*1/NI*	*Erythroderma*	*Continued*	*Local + acitretin*	*Improved*
15	M, 65,2	Yes	Plaque	Lung cancer	Atezolizumab	1/15	Plaque	Continued	Phototherapy	Improved
16	M, 61.7	No	–	Lung cancer	Nivolumab	10/133	Plaque	Continued	Local	No information
17	F, 62.8	No	–	Lung cancer	Nivolumab	6/55	Plaque	Continued	Local + acitretin	Worsened[b]
18[7]	*M, 80*	*No*	–	*Melanoma*	*Nivolumab*	*4/63*	*Plaque*	*Stopped*	*General CS*	*Improved*
19	M, 76.3	No	–	Melanoma	Nivolumab	2/21	Plaque	Continued	Local	Improved
					Pembrolizumab	NI	Plaque	Continued	Local	Improved
20	M, 58,9	No	–	Melanoma	Pembrolizumab	12/229	Plaque/PPP	Continued	Local	Improved
21	M, 77.3	No	–	Melanoma	Pembrolizumab	2/42	Plaque/guttate	Continued	Local	Improved

Cases 16–19 were cases previously published. Cases in italic: cases reported in the literature references.
[a]Delay between first injection of anti-PD1 treatment and psoriasis flare.
[b]Case 11. Patient rapidly died after initiation of anti-PD1. Case 16. Because of the severity of psoriasis, anti-PD1 was finally stopped, and the patient treated with general corticosteroids.
M, male; F, female; PuPPP, pustular palmoplantar psoriasis; PPP, palmoplantar psoriasis; NI, no information; CS, corticosteroid.

characteristics of anti-PD1-induced psoriasis. The study was performed in two steps: evaluation of cases; then systematic review of the literature.

From November to December 2015, we performed a multicentre study asking members of five national associations of dermatologists and a national cooperative group of lung specialists involved in lung cancer clinical research to report anti-PD-1 induced psoriasis. The protocol for evaluation included items on patients, psoriasis, cancer, anti-PD1. Bibliographic search was conducted on MEDLINE using PUBMED as the query interface using the key words: 'psoriasis' and 'nivolumab'; or 'pembrolizumab', 'atezolizumab', 'pidilizumab' and 'anti-PD1'.

We included 17 patients who received 18 anti-PD1 treatments. Literature review found four patients.[5–8] Final analysis included 21 patients who received 22 anti-PD1 treatments (Table 1). Eighteen (85.7%) patients were males, mean age 64.8 ± 12.6 years. Fifteen (71.4%) had a history of psoriasis. Clinical types were plaque (53.3%), scalp (20.0%), guttate (20.0%) psoriasis, or sebopsoriasis (6.8%). Four (26.6%) had been treated with general treatments (phototherapy, $n = 2$; acitretin, $n = 2$). In all the cases, the psoriasis was considered as mild and controlled by topical treatments before initiation of anti-PD1 treatment (Table 1). Eleven (52.4%) patients had melanoma and 10 (47.6%), lung cancer. Two (10.5%) received the anti-PD1 as first-line therapy, and 17 (89.5%) as 2nd-line or more (no information for two patients). Fifteen (72.1%) received nivolumab, 6 (28.6%) pembrolizumab, and 1 (4.8%) atezolizumab. Case 17 received nivolumab and pembrolizumab (Table 1). Anti-PD1 of seventeen (81.0%) patients was maintained despite psoriasis flare. Delay between introduction of anti-PD1 and psoriasis flare was 50.1 ± 51.5 days, higher in the group with *de novo* psoriasis (90.5 ± 77.7 vs. 32.8 ± 21.8, $p = 0.1$). Twenty (95.2%) patients developed plaque psoriasis (Fig. 1). In cases with plaque type, patients also developed guttate ($n = 6$), palmoplantar ($n = 4$), or pustular palmoplantar ($n = 1$) (Fig. 1) psoriasis. Seventeen (80.9%) patients were treated first by topical treatment, two (9.5%) were treated with systemic steroids, one (4.8%) with acitretin, and one (4.8%) with phototherapy. Among the 17 patients, five needed acitretin to control psoriasis as a second-line therapy. Psoriasis in 19 (90.5%) patients was controlled by the treatment, while in two patients, it worsened despite general treatments (Table 1).

We describe 21 cases of inducted or exacerbated psoriasis in patients on anti-PD1 chemotherapy. A history of psoriasis is the main risk factor to develop psoriasis with anti-PD1; however, history of psoriasis is not necessary for this condition to occur. The timeline to develop psoriasis was shorter if the patients had previous psoriasis. Main clinical type is plaque psoriasis, as in 'healthy' psoriatic patients. The treatment resembles treatment of classical plaque patients. The eruption can be controlled in the majority of cases with topical treatments, steroids and/or vitamin D analogues, and the chemotherapy can be continued.

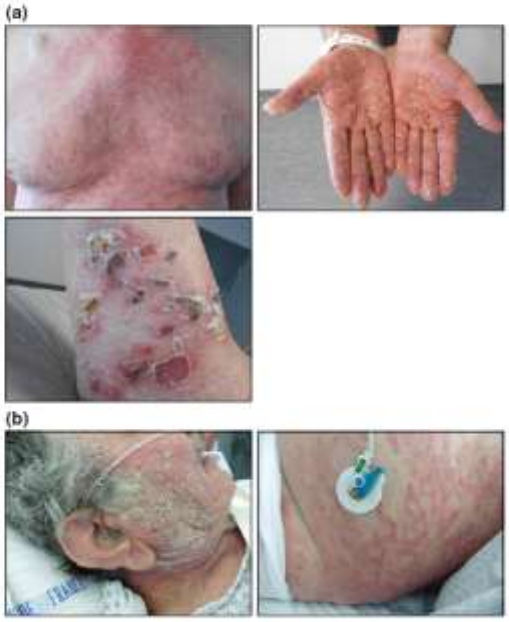

Figure 1 Case 1. (a) Flare 1: first flare of psoriasis, with pustular and plaque components, developed with a toxic rash. Anti-PD1 was maintained and the psoriasis was controlled with topical steroids. (b) Flare 2: After the sixth injection, he came for a severe lung infection, and he developed a second flare of psoriasis, with severe plaque psoriasis. Because of the severity of lung and skin toxicities, the nivolumab was withdrawn.

It is important since anti-PD1 therapy changes the prognosis of melanoma and lung cancer.[1–4] Acitretin or methotrexate can be proposed in resistant psoriasis. Phototherapies can be helpful but have to be discussed in patients with melanoma because of photo-induced skin carcinogenesis. Cyclosporine or biological therapies are not indicated since cancer is a contraindication for these treatments.

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LETTER TO THE EDITOR

Characteristics of patients with plaque psoriasis who have discordance between Psoriasis Area Severity Index and dermatology life quality index scores

Editor

Psoriasis has a major physical, psychological and social impact.[1,2] To evaluate physical disease severity, scores are useful. The most frequently used is the Psoriasis Area Severity Index (PASI) which evaluates lesions according to clinical characteristics. It is restricted to plaque psoriasis.[3–5] The most commonly used score to assess the impact on the quality of life (QoL) is the dermatology life quality index (DLQI).[6] It is widely used, translated in many languages and is considered as a reference to evaluate QoL alteration induced by skin diseases in most of guidelines. In psoriasis, QoL alteration is not always correlated to clinical severity.[5–7] The aim of this study was to evaluate the clinical, demographic and socio-economic characteristics of patients with plaque psoriasis who have discordant results between PASI and DLQI, one high (over 10) and the other low (<10) and vice versa.

'R-ens' study (*Resopso : Evaluation Nationale du parcours de Soins pour un psoriasis*) was a non-interventional, cross-sectional, multicentre study on adults with psoriasis performed in 40 dermatology centres' members of the GEM Resopso from January to December 2014. R-ens was designed to evaluate impact of socio-economic and demographic characteristics of the patients on the severity of psoriasis at a first consultation. All the adults (≥18 years) who consulted for the first time for plaque psoriasis were included. The case report form comprised items on patients, psoriasis (including PASI and DLQI), comorbidities and socio-demographic data. Patients were considered 'discordant' if they had PASI ≤ 10 and DLQI > 10 (Group 1) or PASI > 10 and DLQI ≤ 10 (Group 2).[8]

Table 1 Clinical data and comparisons of discordant groups

	All patients *n* = 749	Group 1 *n* = 131	Group 2 *n* = 124	*P*-value
Age (years)	45.5 ± 16.1	42.2 ± 14.1	48.2 ± 17.4	0.003
Male	433 (57.8)	60 (45.8)	87 (70.2)	<0.0001
Psoriasis				
Age (years) at onset of psoriasis	28.7 ± 16.8	27.2 ± 15.1	28.7 ± 18.0	0.48
Familial psoriasis	305 (41.3)	48 (37.8)	55 (45.5)	0.09
Psoriasis arthritis	124 (16.8)	27 (20.9)	24 (19.7)	0.80
PASI	12.4 ± 9.0	6.9 ± 2.5	18.0 ± 7.7	<0.0001
DLQI	11.3 ± 6.7	15.8 ± 4.2	6.9 ± 2.5	<0.0001
Treatments of psoriasis				
Topical	631 (84.9)	119 (90.8)	106 (88.3)	0.31
Phototherapy	151 (20.3)	34 (26.0)	20 (16.7)	0.06
Systemic	125 (16.8)	26 (19.8)	16 (13.3)	0.15
Alternative treatments	74 (9.9)	14 (10.7)	16 (13.3)	0.56
Comorbidities				
Hypertension	138 (18.4)	19 (14.5)	36 (28.0)	0.005
Dyslipidaemia	112 (15.0)	20 (15.3)	25 (20.2)	0.31
Diabetes	50 (6.7)	7 (5.3)	15 (12.1)	0.05
Depression	83 (11.1)	18 (13.7)	13 (10.5)	0.43
Smoking	313 (41.8)	65 (49.6)	46 (37.1)	0.04
Alcohol consumption	171 (22.8)	23 (17.6)	35 (28.2)	0.04
BMI (kg/m^2)	26.5 ± 5.8	25.6 ± 6.2	27.4 ± 6.2	0.02

Data are expressed as *n* (%) or mean ± standard deviation. Group 1: PASI ≤ 10 and DLQI > 10. Group 2: PASI > 10 and DLQI ≤ 10.
BMI, body mass index; DLQI, dermatology life quality index; PASI, Psoriasis Area Severity Index.

Table 2 Socio-economic and demographic data and comparisons of discordant groups

	All patients $n = 749$	Group 1 $n = 131$	Group 2 $n = 124$	*P*-value
No. of GP seen before the consultation	1.6 ± 2.3	2.2 ± 4.1	1.5 ± 1.3	0.08
No. of dermatologist seen before the consultation	2.2 ± 2.6	2.6 ± 3.9	2.3 ± 2.6	0.59
No. of GP seen during the year before the consultation	0.7 ± 0.8	1.0 ± 1.4	0.7 ± 0.6	0.04
No. of dermatologists seen during the year before the consultation	0.7 ± 0.7	1.0 ± 1.4	0.7 ± 0.6	0.04
Living environment				
Urban	269 (36.4)	29 (22.5)	34 (27.6)	0.39
Semi-urban	271 (36.7)	49 (38.0)	50 (40.7)	
Rural	198 (26.8)	51 (39.5)	39 (31.7)	
Familial structure				
Life as couple	221 (30.5)	38 (29.5)	36 (30.3)	0.89
Children at home	285 (39.9)	54 (42.2)	50 (41.0)	0.84
Working aspects				
Working	578 (78.7)	111 (87.4)	91 (74.0)	0.007
In contact with public	327 (72.8)	82 (84.5)	41 (63.1)	0.002
Sporting activity	262 (35.2)	48 (36.9)	33 (26.8)	0.12
Salary <2300€	320 (52.6)	56 (48.7)	55 (55.0)	0.35
Education level: bechelor or less	475 (64.5)	68 (54.0)	82 (67.2)	0.03

Data are expressed as *n* (%) or mean ± standard deviation. Group 1: PASI ≤ 10 and DLQI > 10. Group 2: PASI > 10 and DLQI ≤ 10.
DLQI, dermatology life quality index; GP, general practitioners; PASI, Psoriasis Area Severity Index; SD, standard deviation.

During this 1-year study, 749 patients were included, and 255 (34.0%) were discordant: 131 (17.5%) in group 1 and 124 (16.6%) in group 2. Characteristics of patients are detailed in Tables 1 and 2. Patients in group 1 were younger ($P = 0.003$), women ($P < 0.0001$), who smoke ($P = 0.04$), with lower BMI ($P = 0.02$). They had seen more general practitioner ($P = 0.04$) and dermatologists ($P = 0.04$). They have more frequently an occupation ($P = 0.007$), in contact with the public ($P = 0.002$), and a higher level of education ($P = 0.03$). Patients in group 2 were older ($P = 0.003$), men ($P < 0.0001$), with hypertension ($P = 0.005$), who drank alcohol ($P = 0.04$) and with higher BMI ($P = 0.02$) (Tables 1 and 2).

Our results showed two distinct profiles of patients. In the group 1, we identified a 'working girl' profile: a young woman working in contact with the public, with a high level of education. In the group 2, we identified a 'lower class man with comorbidities' profile: a man, with hypertension, who drinks alcohol, with a lower level of education.

In clinical trials, a wide range of outcome measures has been used to evaluate the severity of psoriasis and its response to treatments.[4] Although we instinctively understand the concept, defining severe psoriasis is fraught with limits, and the discordance between scores in one-third of cases confirms that there is no 'perfect' score![4] The factors contributing to the concept of psoriasis severity differ depending on the perception of the assessor. From the patient's perspective, psoriasis will be considered severe if it causes embarrassment or if it affects relationships. The role of sex in score discordance has not been shown in previous studies.[6,8] We found that DLQI scored significantly higher in women than in men. This ending could be explained by the association of the general female stereotype with a greater interest in appearances and a greater dependency on social relationships than men. We found also that the patients who have an occupation in contact with the public scored significantly higher, probably for the same reasons. Earlier studies also noted the decreasing impact of disease with age.[9,10] It was confirmed herein.

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Mémoires et thèses (2016)

AGNES GALEZOWSKI
Faculté de Médecine Paris VI – Université Pierre et Marie Curie
Thèse de Doctorat en Médecine, spécialité Dermatologie – Vénéréologie
« EPIDEMIOLOGIE DU RHUMATISME PSORIASIQUE EN FRANCE, DE L'ENFANT A LA PERSONNE AGEE. DONNEES DE DEUX ETUDES TRANSVERSALES FRANÇAISES, DANS UNE POPULATION DE PATIENTS ATTEINTS DE PSORIASIS CUTANE »
Direction : Emmanuel Mahé
Soutenance : 1er avril 2016

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CELINE PHAN
Mémoire de DES de Dermatologie-Vénéréologie. Région Ile de France
« PSORIASIS IN THE ELDERLY: EPIDEMIOLOGICAL AND CLINICAL ASPECTS, AND EVALUATION OF PATIENTS WITH VERY LATE ONSET PSORIASIS »
Direction : Emmanuel Mahé
Soutenance : 16 septembre 2016

Appels à cas au sein du GEM

Biothérapie chez les patients hémodialysés (2014) – Resopso, Gr Pso SFD
Coordination : J.-L. Schmutz, Nancy
Nombre d'inclusions : 5
Article soumis :
Larquey M, Girard C, Sbidian E, Richard MA, Aubin F, Schmutz JL. Efficacy of biologics in psoriasis patients under hemodialysis.

Partenariats du GEM

Psoriasis segmentaires (2015)
« PSORIASIS SEGMENTAIRES. ETUDE NATIONALE »
Etude Groupe de Recherche sur le Psoriasis de la SFD / Société Française de Dermatologie Pédiatrique
Investigateur principal : E. Mahé

RISQUES INFECTIEUX SIMILAIRES ENTRE ANTI-TNFA ET THERAPIES SYSTEMIQUES CLASSIQUES DANS LE PSORIASIS

Garcia-Doval I, Cohen AD, Cazzaniga S, et al
Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-rumor necrosis factor agents versus classic therapies: prospective meta-analysis of Psonet registries.
J Am Acad Dermatol 20016 [Epub ahead of print]

De nombreuses données suggèrent que les anti-TNF a sont associés à un risque accru d'infections graves, que ceux-ci soient utilisés dans la polyarthrite rhumatoïde (PR) ou dans le psoriasis.

Des études observationnelles ont été mises en place pour surveiller le profil de sécurité de ces biologiques en pratique clinique.

Pour évaluer le risque potentiel des anti-TNF a par rapport aux traitements systémiques classiques utilisés dans le psoriasis (acitrétine, méthotrexate, ciclosporine), Garcia-Doval I et al ont utilisé trois registres du réseau Psonet. Il s'agit, en Espagne, du registre Biobadaderm débuté en 2008 regroupant 13 hôpitaux. En Israël, il s'agit du registre Clalit Health Service qui intègre les patients traités par un systémique dans une population de 4,4 millions d'individus enregistrés. Enfin, en Italie, il s'agit du registre Psocare activé de septembre 2005 à septembre 2009. Les auteurs ont effectué une méta-analyse des données de ces registres. Ils ont analysé les dossiers de 17 739 patients correspondants à un suivi total de 23 357 patients-années : 7 664 patients étaient traités par infliximab (Remicade®), adalimumab (Humira®) ou étanercept (Enbrel®) ; 10 095 recevaient un traitement systémique conventionnel (acitrétine, méthotrexate ou ciclosporine).

L'analyse ajustée selon le sexe, l'âge et l'indice de morbidité de Charlson indique que le risque d'infections sévères associées aux anti-TNF a était multiplié par un facteur de 0,98 (95% IC 0,80-1,19) par rapport aux traitements systémiques conventionnels, sans différence statistiquement significative.

De manière similaire, le risque d'infection bactérienne cutanée était de 1,00 (95% IC 0,62-1,61) et celui des infections granulomateuses (notamment tuberculeuses) était de 1,23 (95% IC 0,82- 1,84) toujours sans différence significative. Les résultats étaient similaires en limitant la comparaison au méthotrexate. Les données étaient insuffisantes pour comparer les anti-TNF a individuellement.

Au total, l'étude de Garcia-Doval I, et al tend à montrer qu'en pratique clinique, les anti-TFN a ne présentent pas un sur-risque d'infections graves par rapport aux thérapies systémiques conventionnelles.

Rubrique rédigée par J.-L. Schmutz

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