Traitements systémiques des dermatoses inflammatoires

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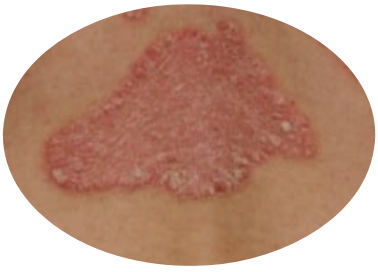
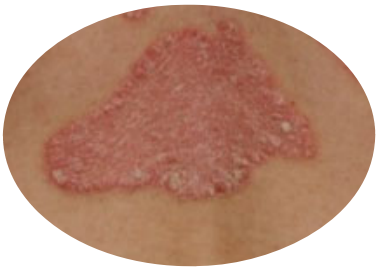
Dermatoses inflammatoires…

Psoriasis en plaques



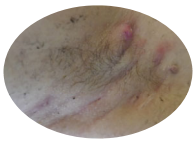
Dermatoses inflammatoires…

Psoriasis en plaques



Psoriasis en plaques

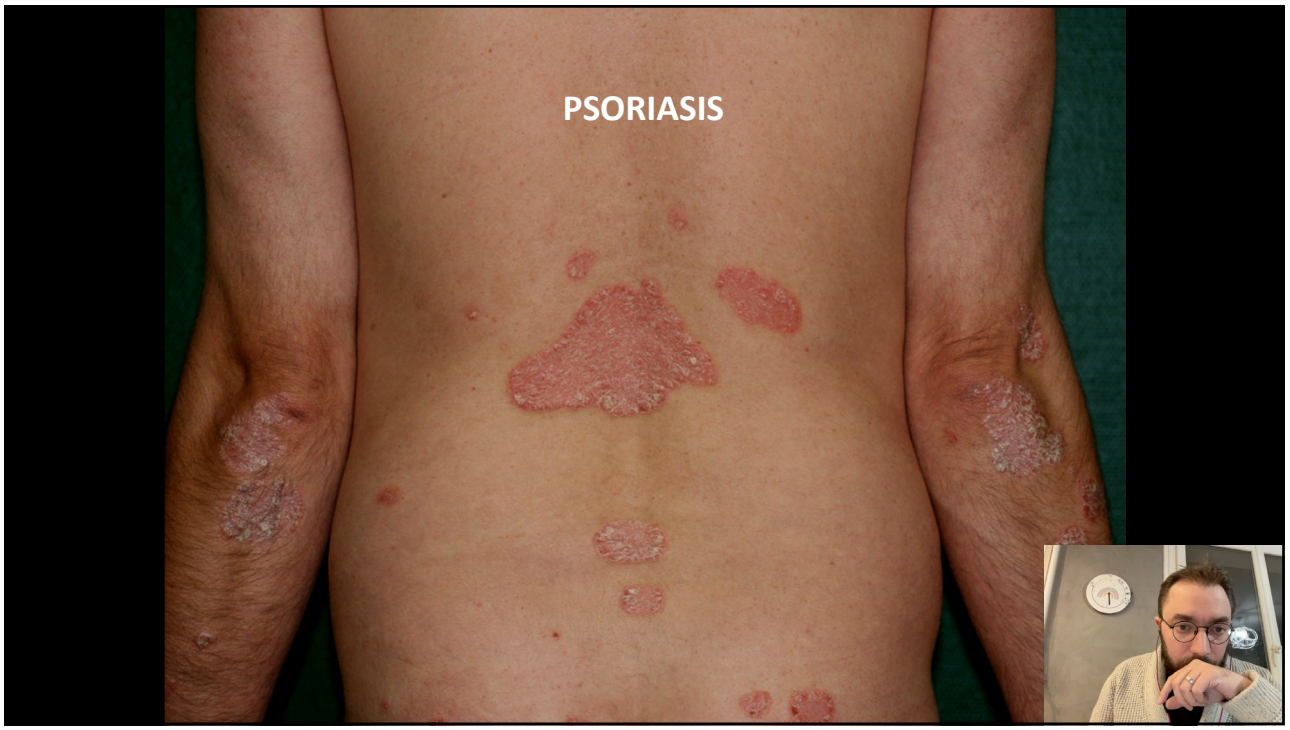
Hidradénite suppurée

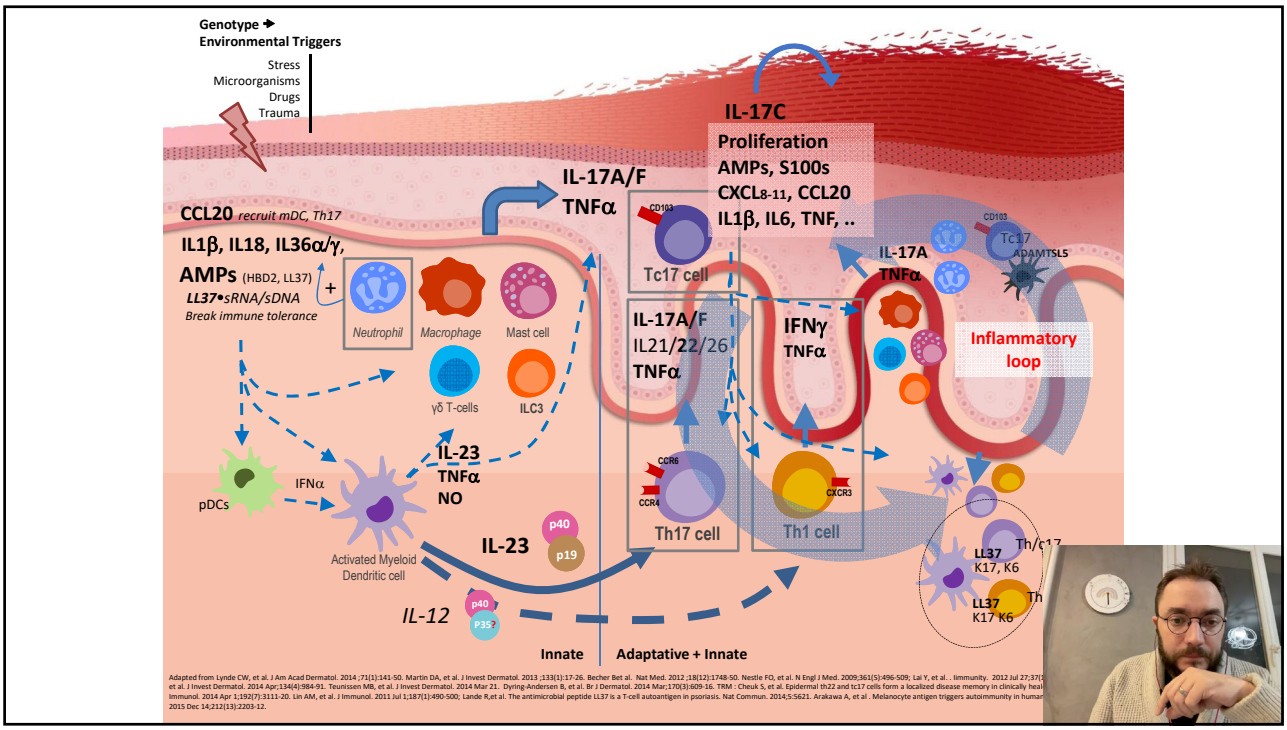


Dermatoses éosinophiliques

Dermatoses neutrophiliques

Lupus érythémateux cutané





Adapted from Lynde CW, et al. J Am Acad Dermatol. 2014 ;71(1):141-50. Martin DA, et al. J Invest Dermatol. 2013 ;133(1):17-26. Becher Bet al. Nat Med. 2012 ;18(12):1748-50. Nestle FO, et al. N Engl J Med. 2009;361(5):496-509; Lai Y, et al. . Iimmunity. 2012 Jul 27;37(

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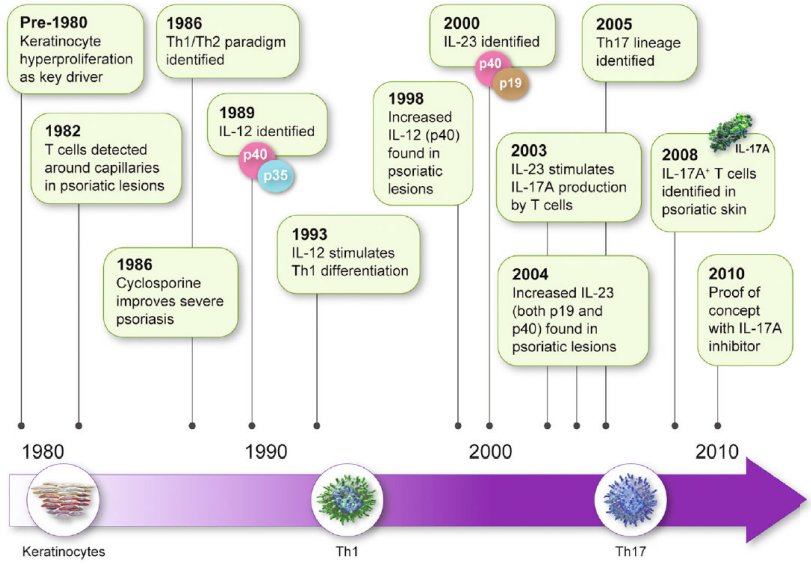
Psoriasis et populations lymphocytaires T effectrices



Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: Toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014 Mar 18.

Recommandations et stratégies thérapeutiques - psoriasis en plaques

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OPINION D'EXPERT

Recommandations françaises sur l'utilisation des traitements systémiques chez les patients adultes atteints de psoriasis modéré à sévère

French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults

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GUIDELINES

EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Part 1: treatment and monitoring recommendations

A. Nast,[1,*] C. Smith,[2] P.I. Spuls,[3] G. Avila Valle,[1] Z. Bata-Csörgö,[4] H. Boonen,[5] E. De Jong,[6] I. Garcia-Doval,[7] P. Gisondi,[8] D. Kaur-Knudsen,[9] S. Mahil,[10] T. Mälkönen,[11] J.T. Maul,[12] S. Mburu,[13] U. Mrowietz,[14] K. Reich,[15] E. Remenyik,[16] K.M. Ronholt,[17] P.G. Sator,[18] M. Schmitt-Egenolf,[19] M. Sikora,[20] K. Strömer,[21] O. Sundnes,[22] D. Trigos,[13] G. Van Der Kraaij,[3] N. Yawalkar,[23] C. Dressler[1]

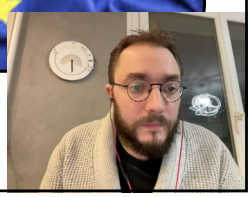
Quand débuter un traitement systémique ?

Recos France

- **BSA > 10 %**
- **OU PASI > 10 ET/OU DLQI >10**
- **Retentissement important de la maladie (anxiété/dépression)**
- **Psoriasis localisé non contrôlé par des topiques (ongles, atteintes génitales, palmoplantaire, cuir chevelu…)**

Recos Europe

- **BSA > 10 % ET PASI > 10 ET DLQI 10**
- **Psoriasis localisé non contrôlé et s'aggravant malgré un traitement topique bien conduit**
  - **Topographie : ongles, atteinte génitale, palmoplantaire, cuir chevelu…**
  - **Prurit sévère et/ou persistance de plaques récalcitrantes**



1. *Nast A, et al. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498.*
2. *Amatore F, et al. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):464-483.*
3. *Amatore F, et al. Ann Dermatol Venereol. 2019 Jun-Jul;146(6-7):429-439*

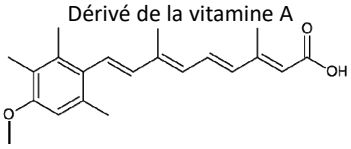
Photothérapie

- Traitement consistant en l'irradiation du corps par des rayons UVB ou UVA dans des cabines spécifiques
  - Mode d'action ?
  - Action immunosuppressive ?
  - Rôle du microbiote cutané et des peptides antimicrobiens ?
- PUVA + photosensibilisant, UVB sans photosensibilisant
- Approx. 200 séances/vie
- Contraintes liées au déplacement et à la fréquence des séances
- Risque de cancers cutanés +++
  - Contre-indication formelle en cas d'antécédent de mélanome, contre-indication relative en cas d'antécédent de carcinome cutané
- Attention aux médicaments photosensibilisants
- Protection OGE/yeux

Acitrétine

- Posologie de départ : entre 10 et 25mg/jour
- A S4, on peut augmenter de 10mg tous les 15 jours jusqu'à l'apparition des signes d'imprégnation (chéilite)
- Pas de différence significative entre une dose d'induction de 25 ou de 35 et 50mg
- Evaluation de l'efficacité pas avant 3-6 mois
- Posologie d'entretien entre 25 et 50mg/jour

Dérivé de la vitamine A

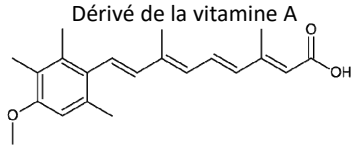


- 2 études ont évalué l'acitrétine vs étanercept =>supériorité de l'étanercept
- Combinaison :
  - TTT topique recommandée
  - MTX : possible mais non recommandé
  - Etanercept : tolérance ok et possiblement efficacité augmentée

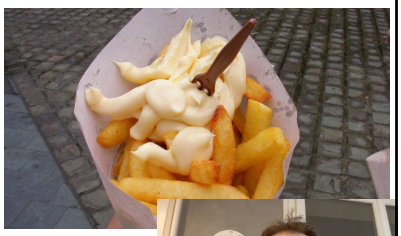
Caproni M et
Dogra S et al., J Eur Acad
Gisondi e
Rim JH et al.
Van de Kerkhof PC e

Acitrétine : précautions d'emploi

Dérivé de la vitamine A



- Pas de GROSSESSE :
  - Double contraception : préservatifs/pilule ou IUD/nuva ring
  - Eviter pilule progestative microdosée pendant toute la durée du traitement et 2 ans après
  - Surveillance mensuelle H/F - βhCG
- Pas d'alcool -> diminuer la toxicité hépatique/ Pas de don du sang
- Xérose cutanée : stick lèvres – pas de lentilles de contact
- ATTENTION associations :
  - Tetracyclines : HTIC
  - MTX-imidazolés : toxicité hépatique cumulative
  - Phénytoïne : diminution du taux plasmatique
  - Pilule contraceptive progestative : diminution de l'éfficacité
- A prendre au cours d'un repas gras ou avec du lait entier



European S3-Guidelines on the systemic treatment of

Acitrétine : surveillance biologique

- **Préthérapeutique : NFP/BH/fct° rénale/bétaHCG/glycémie/EAL**
- **ASAT, ALAT : peu hépatotoxique en l'absence de FdR (obésité, stéatose)**
  - **M1, M2 puis tous les 2 mois si N, sinon mensuel**
- **Cholestérol total et triglycérides :**
  - **Augmentation progressive du cholestérol**
  - **Augmentation parfois brutale des triglycérides -> pancréatite ?**
  - Contrôle M1, si N tous les 3 mois, si anormal tous les mois
  - Régime +- hypolipémiants ou diminution de la posologie
  - TG>5 mmol/L ou 3g/L -> ARRET DU TTT
- **Surveillance NFP tous les 2 mois**
- **bétaHCG mensuel**

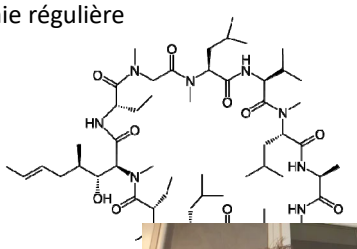
European S3-Guidelines on the systemic treatment of

Ciclosporine

Poids idéal – formule de Devine
Poids idéal Homme (kg) = 49,9 + 0,89 (taille en cm – 152,4)
Poids idéal Femme (kg) = 45,4 + 0,89 (taille en cm – 152,4)

- Inhibiteur de la calcineurine
- Prescription initiale hospitalière de 6 mois

- Posologie initiale : 2,5 -3 mg/kg/jour (poids idéal) en 2 doses (parfois 5mg/kg/j pour effet rapide)
- TA mesurée à 2 reprises en préthérapeutique, surveillance TA, créatininémie régulière



Evaluation du traitement :

- Traitement rapidement efficace
- S4 : si besoin pour l'adaptation des doses
- Entre la semaine 10 – 16 :
  - A 5mg/kg/jour, PASI 75 : entre 50 et 97 %
  - A 2,5mg/kg/jour, PASI 75 : entre 28 et 85 %

Maza et al. J Eur Aca
Paul et al. Ar

Ciclosporine : précautions et effets secondaires

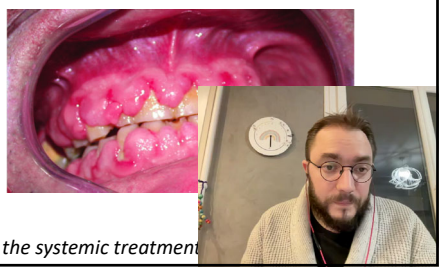
- Eviter les facteurs de risque de toxicité rénale :
  - HTA – élévation de la créatininémie de base, âge>50 ans
  - Doses>5mg/kg/j
  - -> privilégier traitement intermittent 3-6 mois
- Arrêt brutal sans décroissance
- Autorisé chez la femme enceinte

- Préthérapeutique :
  - Sérologies HIV, HBV, HBC
  - bétaHCG
  - NFP
  - ASAT/ALAT
  - Acide urique
  - Ionogramme sanguin, Fonction rénale
- Effets secondaires :
  - Insuffisance rénale : jusqu'à 20% patients
  - HTA : 2-15% patients
  - Nausées/diarrhées : 10-30%
  - Cytolyse hépatique 30%
  - ↗Risque de Covid sévère

European S3-Guidelines on the systemic treatment of

Ciclosporine : CAT devant des effets secondaires

- **Elévation de créatininémie>30%**
  - Diminution de la posologie de 30% + contrôle
  - Persistance = ARRET
- **HTA**
  - RHD
  - IEC ou Inhibiteurs calciques en 1ère intention (excepté diltiazem)
- Hypertrophie gingivale
  - Soins bucco-dentaires – détartrage
- Hypertriglycéridémie : RHD



European S3-Guidelines on the systemic treatment

Méthotrexate

- <u>Posologie habituelle : 15-20mg/semaine</u>
  - Ancien schéma d'initiation dermatologique : 5, 10, 15, 20mg
  - Schéma d'initiation rhumatologique : 15mg/sem d'emblée puis 20mg/sem
  - Schéma actuel : 17,5mg/sem, réévaluation à M2 et augmentation à 22,5mg/sem si réponse<PASI50
- <u>Données d'efficacité</u>
  - **de 5, 15 mg puis 20 mg → PASI 75 : 30-40 % à S16**
  - **de 15 - 22,5 mg → PASI 75 : 60 % à S16**
- **Evaluation de l'efficacité :**
  - Max en 12 à 20 semaines -> 4 mois
  - Réponse insuffisante -> augmentation jusqu'à 25mg/S ou SC
  - Pas de réponse à 20mg/S -> pas d'intérêt à augmenter

Saura
Reid
Dogra S et
Mrowietz U et al., J E

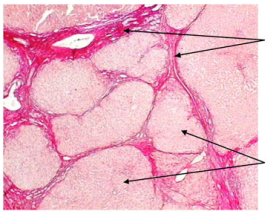
Méthotrexate : gestion des effets secondaires

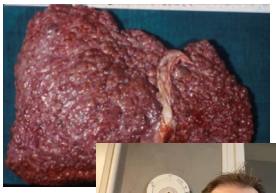
- <u>ACIDE FOLIQUE en systématique</u>
  - Tolérance digestive ++
  - Cytolyse hépatique
  - Plusieurs schémas d'administration possibles
    - Consensus : 5mg 24 heures après le méthotrexate
- Pneumopathies : précoces par PID, tardives par fibrose pulmonaire
  - Toux persistante
  - Dyspnée
  - Pas de sur-risque pulmonaire infectieux sous MTX
- Tératogénicité :
  - Femme + Homme = contraception et information
- Autres : diminuer les doses

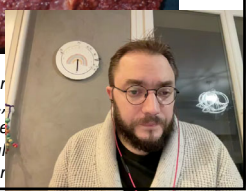
Saura
Reid
Dogra S et
Mrowietz U et al., J E

Méthotrexate : effets au long cours

Initiation	Au long cours
Toxicité hématologique (NFP J5) **Cytolyse hépatique**	**Pas de sur-risque de cancer** **Moins d'accidents cardio-vasculaires** **Pas de sur-risque d'infections graves** **FIBROSE HEPATIQUE** **-> trouver la dose minimale efficace**







Montaudie et al., J Eur
Berends et al.,
Malatjalian é
Nal
Ahlehoff et al., J Eur

Méthotrexate et risque de fibrose hépatique

- **Prévalence 8,5%**
  - Etude N=500 patients – dont 20% de psoriasis
  - **FR de survenue de fibrose : <u>IMC>28 et consommation OH</u>**

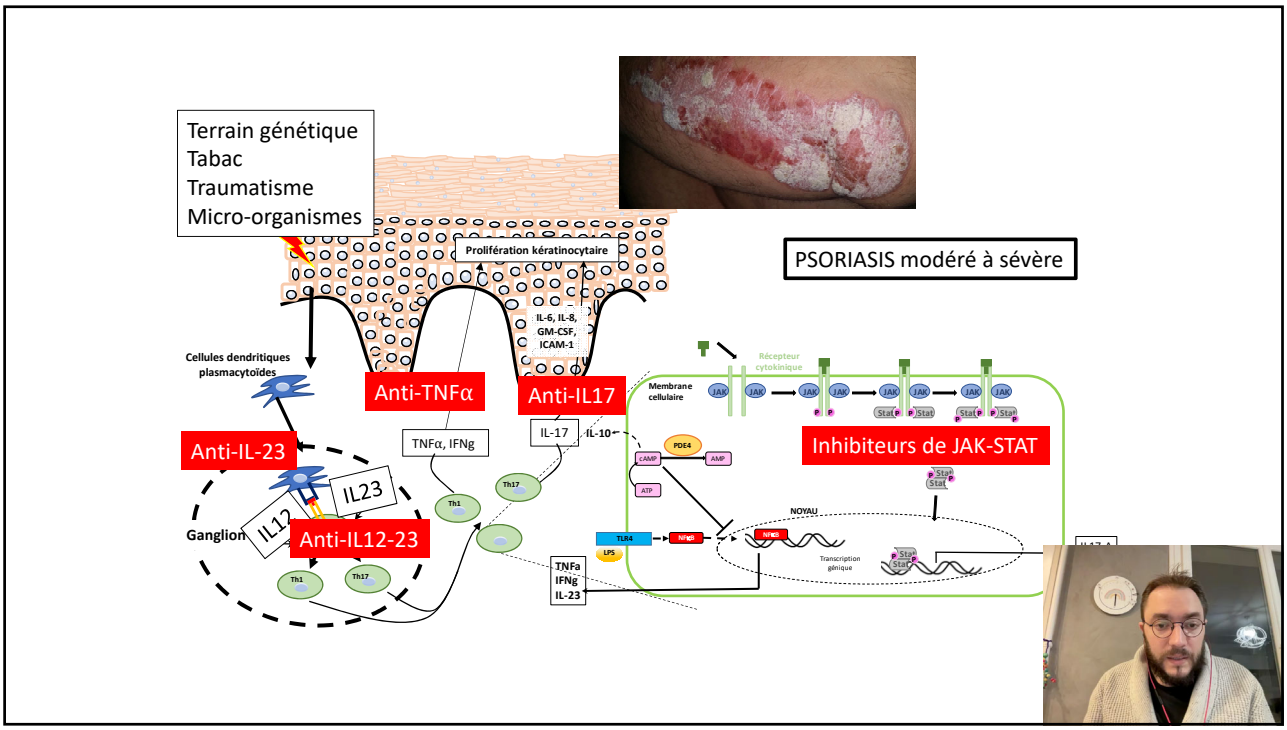
- <u>Surveillance</u> :
  - Procollagen III tous les 6-12 mois
  - Ou Fibroscan -> préthérapeutique chez les patients obèses

Laha
Pathirana D., J E
Nast A et al.,
Beylot-Barry M., Ar

Aprémilast

- **Pas de bilan préthérapeutique**
- **Pas de surveillance biologique sous traitement**
- **Prise orale 30mg matin et soir**
- PASI 75 à S16 -> 33.1%
- Maintien de la réponse PASI 75 à S32 dans 61% des cas, PASI 70 dans 75% des cas
- <u>Effets secondaires :</u>
  - Troubles gastro-intestinaux essentiellement à l'instauration du traitement
  - Syndrome dépressif/idées noires/risque suicidaire -> 1,3% - dépister avant instauration
- Efficacité démontrée versus placebo uniquement – efficacité inférieure aux biothérapies – *versus* M

Papp K et al., J Am Acc



Biothérapies : précautions d'emploi générales

- Prescription initiale hospitalière, renouvellement par dermatologue libéral possible pendant 1 an
- Immunomodulation (*versus* immunosuppression)
- Mise à jour des vaccinations, vaccination contre le pneumocoque (Covid-19 : schéma vaccinal classique)
- Bilan préthérapeutique à la recherche d'une tuberculose latente :
  - Quantiféron
  - Imagerie pulmonaire
- Pour le patient <u>et</u> le médecin généraliste <u>et</u> le pharmacien d'officine
  - Ne pas réaliser l'injection en cas d'infection active/fièvre
  - Bilan à la recherche d'une infection
  - Le traitement peut être repris après la résolution des symptômes
- <u>Grossesse non recommandée : à adapter au cas par cas</u>
  - Arrêt du traitement pour limiter le risque d'immunodépression du nouveau-né

Traitement	Durée d'immuno-dépression du nouveau-né après la dernière injection maternelle
Etanercept	15 jours
Certolizumab	2,5 mois
Adalimumab	
Infliximab	
Ustékinumab	
Sécukinumab	
Ixékizumab Brodalumab Guselkumab Risankizumab	Molécule molécules co

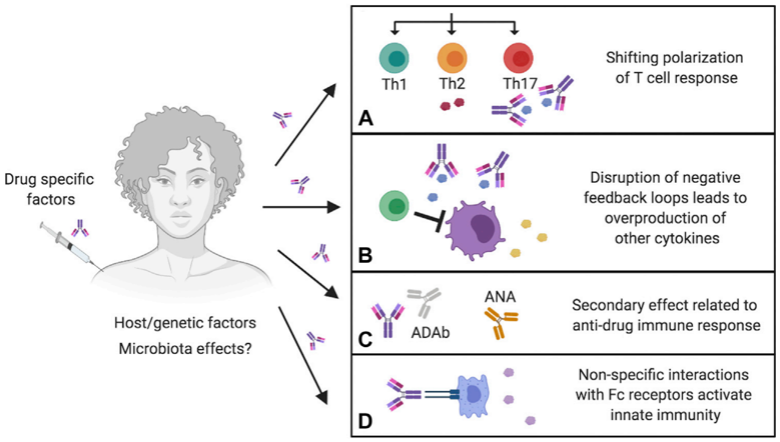
	Infliximab	Adalimumab	Etanercept
Dosing scheme	Intravenous administration (day care hospital unit). 5 mg/kg given at W0, W2, W6, every 8 weeks thereafter (continuous treatment is recommended, Grade A)	s.c. administration. Loading dose of 80 mg at W0, 40 mg W1, then 40 mg every other week.	s.c. administration. 50 mg BIW for up to 12 weeks, followed by 50 mg QW is a more effective strategy than 50 mg QW from the beginning of treatment (Grade A). Possibility of intermittent therapy (grade C). No weight–dose adjustment for obese patients.
Half-life	10 days	2 weeks	70 hours (3 days).
Main adverse events	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, anaphylactic and anaphylactic-like reactions, serum sickness or serum sickness-like reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.
Main contraindications	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infections, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infection, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infection, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.
Surgery	No systematic interruption of INFLI is required prior to minor surgery (Grade C). Discuss interruption of INFLI prior to major surgery (3 to 5 half-lives = 4 to 7 weeks) in patients with a medical history of healing disorders or wound infections (Grade C). Surgery may be placed between two infusions (Expert opinion).	No systematic interruption of ADA required prior to minor surgery (grade C). Discuss interruption of ADA prior to major surgery (3 to 5 half-lives = 6 to 10 weeks) in patients with a past medical history of healing disorders or wound infections (grade C).	No systematic interruption of ETA required prior to minor surgery (Grade C). Discuss interruption of ETA prior to major surgery (3 to 5 half-lives = 9 to 15 days) in patients with a past medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	Around €12 220 for the first year for Remicade® (5 mg/kg W0–W2–W6, then every 8 weeks for an 80 kg patient), not including the day hospital cost. Biosimilars are available (Inflectra®, Remsina®, Flixabi®).	Around €11 400 for the first year for Humira® (80 mg loading dose and 40 mg every other week, starting W1). No biosimilar available in France in 2017.	Around €12 670 for the first year for Enbrel® (50 mg BIW up to W12, followed by 50 Biosimilar available (around €11 140 for the first year for Benepali®).

USTEKINUMAB	
Dosing scheme	s.c. administration. 45 mg at Week 0, Week 4 and then every 12 weeks. Adjusted for patients >100 kg: same scheme, but with a 90 mg dose. Suggested dose-escalation strategy (off-license): USTK 90 mg every 12 weeks (<100 kg) or USTK 90 mg every 8 weeks (>100 kg) (Grade C).
Half-life	3 weeks
Main adverse events	Injection-site erythema, fatigue and muscle/bone pain, diarrhoea, viral, bacterial or fungal infections (no reactivation or new onset of tuberculosis), allergic reactions, exfoliative dermatitis, MACE.
Main contraindications	Active tuberculosis or other serious infection, pregnancy, breastfeeding, active malignancy, hypersensitivity.
Surgery	No systematic interruption of USTK required prior to minor surgery (Grade C) Discuss interruption of USTK prior to major surgery (3 to 5 half-lives = 9 to 15 weeks) in patients with a past medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	Around €14 920 for the first year for Stelara® (45 or 90 mg W0, W4, then every 12 weeks) No biosimilar available in France in 2017.

	SECUKINUMAB	IXEKIZUMAB	BRODALUMAB
Dosing scheme	**s.c. administration: 300 mg, delivered in two injections of 150 mg each. 300 mg at W0, 1, 2, 3, 4 and then 300 mg every 4 weeks. No weight–dose adjustment.**	s.c. administration. Loading dose of 160 mg, 80 mg every other week until week 12, then 80 mg every 4 weeks. No weight–dose adjustment.	s.c. administration. 210mg W0, W1 and then every 2 weeks
Half-life	**27 days**	13 days	11 days
Adverse events	**Infections (upper respiratory tract, candida), diarrhoea, neutropenia, inflammatory bowel disease onset and flare.**	Infections (upper respiratory tract, candida), injection site reactions, neutropenia, inflammatory bowel disease onset and flare.	Infections (upper respiratory tract, candida), injection site reactions, neutropenia, inflammatory bowel disease onset and flare.
Main contraindications	**Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.**	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.
Precautions	**Avoid if possible in patients with a history of inflammatory bowel disease** (Grade C). **Close monitoring of patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (possible class effect -** Expert opinion). **In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk –** Expert opinion).	Avoid if possible in patients with a history of inflammatory bowel disease (**Grade C**). Close monitoring of patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (possible class effect - **Expert opinion**). In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk – **Expert opinion**).	Avoid if possible in patients with a history of inflammatory bowel disease (**Grade C**). Close monitoring of patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (possible class effect - **Expert opinion**). In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk – **Expert opinion**).
Vaccination	**Follow the French immunisation schedule Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.**	Follow the French immunisation schedule. Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.	Follow the French immunisation schedule. Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	**No data available about surgery. We recommend interrupting SEC 4 weeks before performing scheduled surgery. Resume medication after healing (American College of Rheumatology and American Association of Hip and Knee Surgeons recommendations).**	No data available about surgery. We recommend interrupting IXE 4 weeks before performing scheduled surgery. Resume medication after healing (American College of Rheumatology and American Association of Hip and Knee Surgeons recommendations).	No data available about surge before performing scheduled (American College of Rheuma Knee Surgeons recommenda
Cost in France (2017)	**Cosentyx®: First year: €19 375,58, then €14 857/year. No biosimilar available in 2017.**	Taltz®: First year: €18 532, then €13 421/year No biosimilar available in 2017.	Kyntheum® : 998€/2 doses No biosimilar available in 201

	Guselkumab	Risankizumab	Tildrakizumab
Dosing scheme	**s.c. administration: 100mg W0, W4 and then every 8 weeks**	s.c. administration : 150mg W0, W4 and then every 12 weeks	s.c. administration : 100mg W0, W4 and then every 12 weeks
Half-life	**15-18 days**	28 days	20-28 days
Adverse events	**Infections (upper respiratory tract, candida), diarrhoea.**	Infections (upper respiratory tract, candida), injection site reactions	Infections (upper respiratory tract, candida), injection site reactions
Main contraindications	**Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.**	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.
Precautions	**In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk).**	In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk).	In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk).
Vaccination	**Follow the French immunisation schedule Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.**	Follow the French immunisation schedule. Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.	Follow the French immunisation schedule. Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vacc vaccines are contraindicated
Cost in France (2017)	**TREMFYA®: 1800€/dose**	Skyrizi®: 2700€/dose	ILUMETRI® : 2400€/dose

Effets secondaires de mécanismes immunologiques des biothérapies – mécanismes ?



Murphy MJ et

Effets secondaires de mécanismes immunologiques des biothérapies anti-TNFα

Features	Psoriasis (N = 1051)	Eczema (N = 267)	Lupus-like (N = 216)	Sarcoidosis-like (N = 91)	Alopecia areata (N = 66)	Vitiligo (N = 60)	Hidradenitis suppurativa (N = 37)	Lichenoid (N = 33)	Granuloma annulare (N = 14)	Bullous pemphigoid (N = 13)	Dermatomyositis (N = 11)	Pyoderma gangrenosum (N = 10)
Demographic characteristics							n = 37	n = 33	n = 14	n = 13	n = 11	n = 10
Female sex, %	59, n = 926	56, n = 68	81, n = 102	61, n = 90	49, n = 63	37, n = 38	81	60	82	61.5	73	70
Age, y, mean (range)	42.2 (8-83), n = 684	44.6 (15-83), n = 35	42 (14-78), n = 80	48.2 (7-81), n = 89	37.4 (20-69), n = 58	49 (24-83), n = 14	35 (17-57)	47.2 (8-71)	44.5 (23-76)	62.9 (45-81)	41.2 (29-52)	49.2 (40-58)
Drug indication, %	n = 985	n = 240	n = 205	n = 91	n = 66	n = 40	n = 37	n = 33	n = 14	n = 13	n = 11	n = 10
Psoriasis/psoriatic arthritis	5.5	5	1	14	29	7.5	11	30	7	31	9	40
Crohn's disease	39	18	35	—	15	22.5	49	12	—	—	9	—
Ulcerative colitis/ indeterminant colitis	7	4	8	—	1.5	10	—	6	—	31	—	20
IBD (unspecified)	10	65	4	7	10.5	—	—	9	7	—	—	—
Ankylosing spondylitis	17	3	0.5	17	8	47.5	13.5	6	—	—	—	—
Rheumatoid arthritis	15	5	49	57	15	7.5	13.5	24	79	38	54.5	30
Juvenile idiopathic arthritis	0.5	0.4	0.5	4	1.5	—	8	3	—	—	9	—
Hidradenitis suppurativa	0.1	—	—	—	—	2.5	—	—	—	—	—	10
Seronegative spondyloarthritis	5.5	—	—	—	—	—	—	—	—	—	—	—
Seronegative inflammatory arthritis	0.1	—	—	—	—	—	—	—	—	—	9	—
Spondyloarthritis	0.1	—	—	—	1.5	—	—	—	7	—	—	—
Behcet disease	0.4	—	—	—	1.5	—	—	3	—	—	—	—
SAPHO	0.2	—	—	1	—	—	3	—	—	—	—	—
Still's disease	—	—	0.5	—	—	—	—	—	—	—	—	—
Toxic epidermal necrolysis	—	—	—	—	—	—	—	3	—	—	—	—
Oligoarthritis	—	—	—	—	—	—	—	3	—	—	—	—
Pityriasis rubra pilaris	—	—	—	—	—	2.5	—	—	—	—	—	—
Dermatomyositis/ rheumatoid arthritis overlap syndrome	—	—	—	—	—	—	—	—	—	—	9	—
Ankylosing spondylitis/ rheumatoid arthritis	—	—	—	—	—	—	3	—	—	—	—	—

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Effets secondaires de mécanismes immunologiques des biothérapies anti-IL17

Features	Eczema (N = 26)	Psoriasis (N = 15)	Sarcoidosis-like (N = 5)	Alopecia areata (N = 4)	Pyoderma gangrenosum (N = 4)	Lichenoid (N = 4)	Behcet syndrome (N = 3)	Hidradenitis suppurativa (N = 3)	Granuloma annulare (N = 2)	Lupus-like (N = 2)	Vitiligo (N = 2)	Erythema multiforme (N = 1)	Bullous pemphigoid (N = 1)	Pemphigus (N = 1)
Demographic characteristics	n = 15	n = 15	n = 5	n = 4	n = 4, n = 3	n = 4	n = 3	n = 3	n = 2	n = 2	n = 1	n = 1	n = 1	n = 1
Female sex, %	40	67	40	50	100	25	0	0	100	0	0	100	100	100
Age, y, mean (range)	51.2 (23-89)	49 (22-76)	51.6 (45-61)	53.3 (40-70)	42.3 (38-47)	57.8 (45-74)	39.7 (29-56)	50.7 (46-58)	64.5 (60-69)	50.5 (39-62)	48	65	65	41
Drug indication, %	n = 26	n = 15	n = 5	n = 4	n = 4	n = 4	n = 3	n = 3	n = 2	n = 2	n = 1	n = 1	n = 1	n = 1
Psoriasis/ psoriatic arthritis	100	93	100	100	100	75	33	100	100	100	100	—	100	—
Ankylosing spondylitis	—	7	—	—	—	—	33	—	—	—	—	100	—	—
Rheumatoid arthritis	—	—	—	—	—	—	—	—	—	—	—	—	—	100
Ankylosing spondylitis/ Behcet syndrome	—	—	—	—	—	—	33	—	—	—	—	—	—	—
Rheumatoid arthritis/ psoriasis	—	—	—	—	—	25	—	—	—	—	—	—	—	—
Drug, %	n = 26	n = 15	n = 5	n = 4	n = 4	n = 4	n = 3	n = 3	n = 2	n = 2	n = 1			
Secukinumab	42	60	40	50	75	100	100	67	100	100	50			
Ixekizumab	58	20	60	25	—	—	—	33	—	—	50			
Brodalumab	—	20	—	25	25	—	—	—	—	—	—			
Time to onset, mo	n = 15	n = 12	n = 2	n = 4	n = 4	n = 4	n = 3	n = 3	n = 2	n = 2	n = 1			
Mean (range)	3.8 (0.14-8)	4.9 (0.75-16)	19.6 (3.25-36)	6.8 (2-13)	4.2 (0.5-10)	3.6 (<0.25-8)	1.25 (0.75-2)	3.2 (0.5-6)	3.25 (0.5-6)	1.5 (1-2)	3			

Switch phénotypique Th17 → Th2 – lésions eczématiformes

Clinical and histopathological characterization of eczematous eruptions occurring in course of anti il-17 treatment: a case series and review of the literature

G. Caldarola, F. Pirro, A. Di Stefani, M. Talamonti, M. Galluzzo, S. D'Adamio, M. Magnano, N. Bernardini, P. Malagoli, F. Bardazzi, C. Potenza, L. Bianchi, K. Peris & C. De Simone

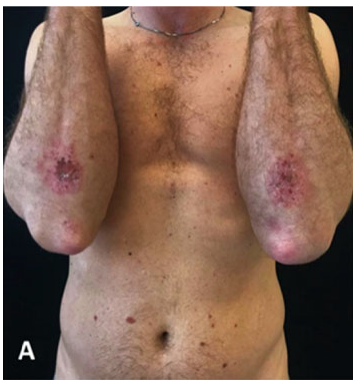
REVIEW ARTICLE

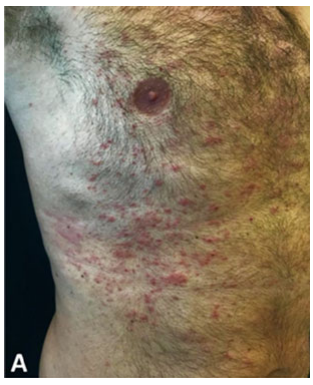
Phenotypic switch to eczema in patients receiving biologics for plaque psoriasis: a systematic review

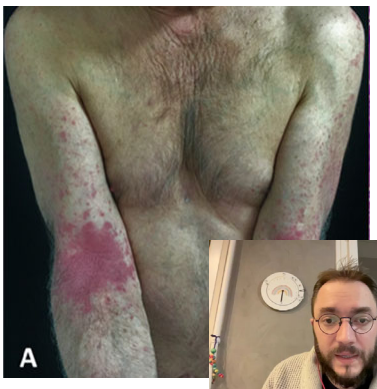
A. Al-Janabi,[1,2,*] A.C. Foulkes,[1,2] K. Mason,[2] C.H. Smith,[3,4] C.E.M. Griffiths,[1,2] R.B. Warren[1,2]

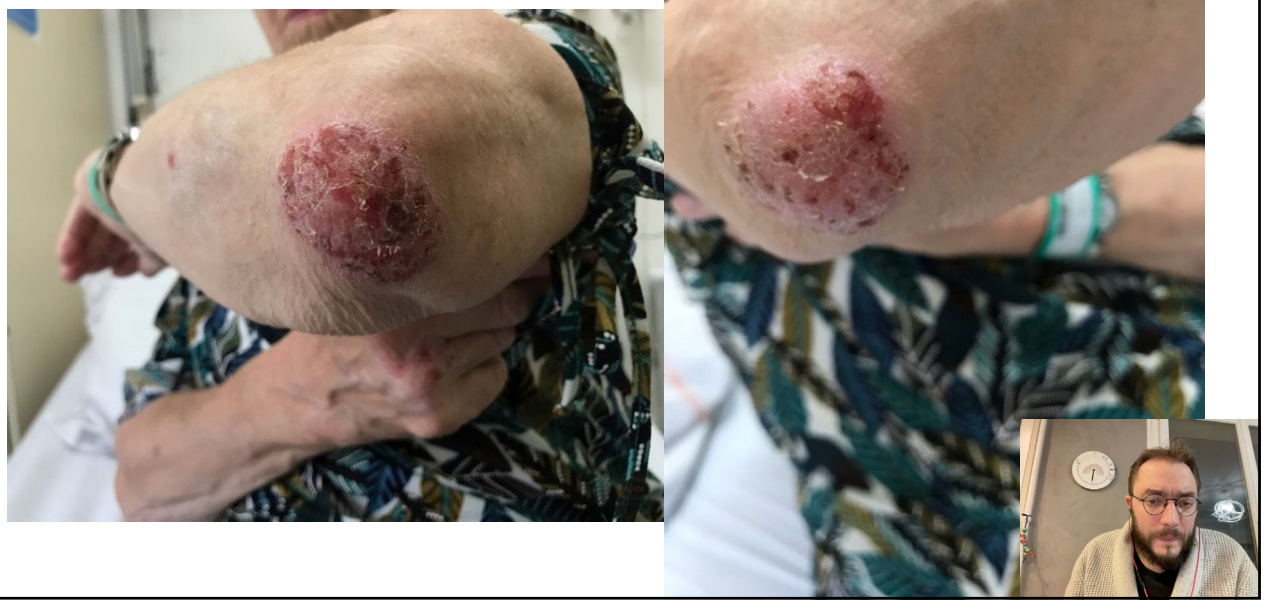
Eczematous eruption during anti-interleukin 17 treatment of psoriasis: an emerging condition

DOI: 10.1111/bjd.17779









Rhinite croûteuse sous biothérapies (anti-TNFα ou anti-IL17)
Infected dermatitis

- Lésions péri-orificielles – vestibule narinaire ± lésions du cuir chevelu
- Inflammation croûteuse
- Erosions suintantes des plis (switch phénotypique Th2 ?)

- Rechercher portage *S. aureus*

- **<u>Traitement double :</u>**
  - Antibiothérapie anti-*Staphylococcus aureus*
  - + traitement de l'inflammation cutanée (tacrolimus topique ? Dermocorticoïdes ?)

- **<u>Physiopathologie</u>** ?
  - Rôle de l'IL-17 dans l'immunité anti-staphylococcus aureus
  - ↘Th17 ↗Th2 ↗*S. aureus ?*
  - ↘Th17 ↗*S. aureus* ↗Th2 ?

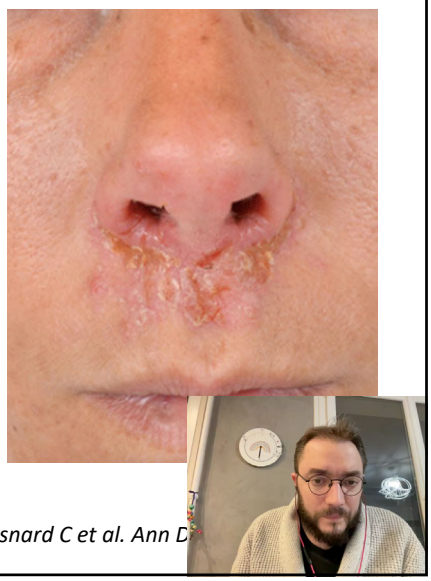


Photo tirée de Mesnard C et al. Ann D

Effets secondaires de mécanismes immunologiques des biothérapies anti-p40 et anti-p19

	IL-12/23												IL-23
Features	Vitiligo (N = 15)	Psoriasis (N = 9)	Alopecia areata (N = 5)	Eczema (N = 4)	Bullous pemphigoid (N = 4)	Sarcoidosis-like (N = 3)	Lupus-like (N = 3)	Morphea (N = 2)	Hidradenitis suppurativa (N = 1)	Frontal fibrosing alopecia (N = 1)	Wells syndrome (N = 1)	Erythema annulare centrifugum (N = 1)	Linear IgA bullous dermatosis (N = 1)	Eczema (N = 2)
Demographic characteristics	NA	n = 9	n = 5	n = 4	n = 4	n = 3	n = 3	n = 2	n = 1	n = 1	n = 1	n = 1	n = 1	n = 2
Female sex, %	NA	67	0	50	25	67	67	100	100	100	0	0	100	0
Age, y, mean (range)	NA	41.7 (24-58)	43 (32-55)	50.3 (21-82)	64.8 (58-76)	48 (42-52)	50.3 (28-68)	55.5 (48-63)	19	62	58	55	31	43.5 (40-47)
Drug indication, %	NA	n = 9	n = 5	n = 4	n = 4	n = 3	n = 3	n = 2	n = 1	n = 1	n = 1	n = 1	n = 1	n = 2
Psoriasis/ psoriatic arthritis	NA	67	100	100	75	100	100	50	100	100	100	100	100	—
Crohn's disease	NA	22	—	—	—	—	—	—	—	—	—	—	—	—
Ankylosing spondylitis	NA	11	—	—	—	—	—	—	—	—	—	—	—	—
Ulcerative colitis	NA	—	—	—	—	—	—	50	—	—	—	—	—	—
Psoriatic onycho-pachydermo-periostitis	NA	—	—	—	25	—	—	—	—	—	—	—	—	—
Psoriasis	NA	—	—	—	—	—	—	—	—	—	—	—	—	100
Drug, %	n = 15	n = 9	n = 5	n = 4	n = 4	n = 3	n = 3	n = 2	n = 1	n = 1	n = 1			
Ustekinumab	100	100	100	100	100	100	100	100	100	100	100			
Guselkumab	—	—	—	—	—	—	—	—	—	—	—			
Time to onset, mo	NA	n = 9	n = 5	n = 2	n = 4	n = 2	n = 3	n = 2	n = 1	n = 1	n = 1			
Mean (range)	NA	3.1 (0.07-15)	6.2 (3-10)	1.25 (1-1.5)	7.8 (1-18)	13 (12-14)	8.8 (1-24)	9 (6-12)	12	5	0.25			

IL, Interleukin; *NA,* not applicable; *PR,* paradoxical reaction.
*The numbers of patients for whom data were available for each specific feature are reported for each section heading.

Mur

Traitements systémiques – recos Françaises 2019

Psoriasis en plaques sans comorbidités – Modéré à Sévère

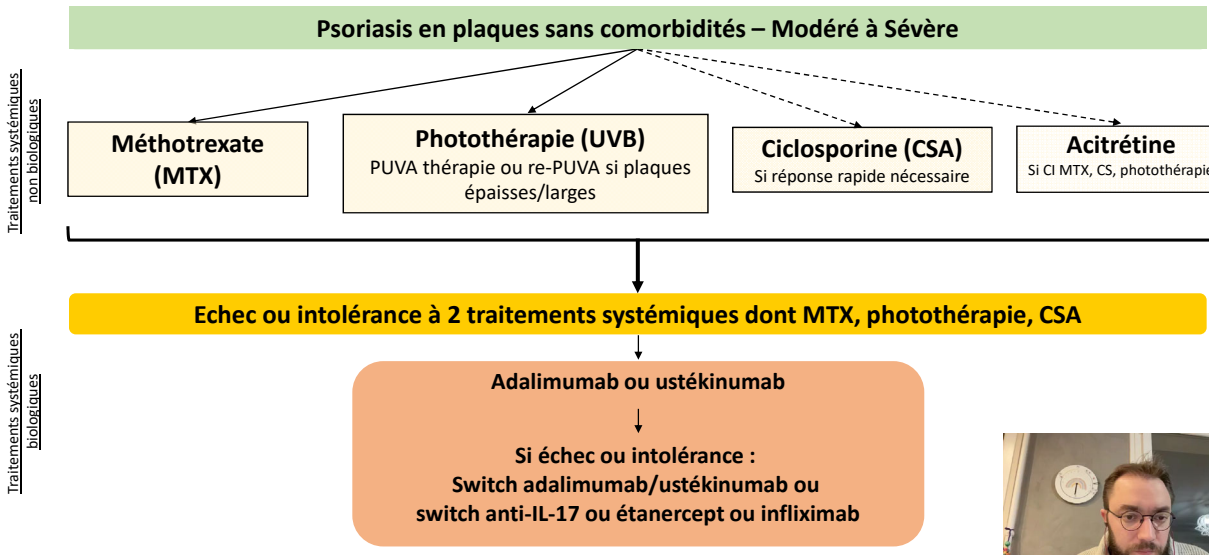
Traitements systémiques non biologiques

- **Méthotrexate (MTX)**
- **Photothérapie (UVB)** — PUVA thérapie ou re-PUVA si plaques épaisses/larges
- **Ciclosporine (CSA)** — Si réponse rapide nécessaire
- **Acitrétine** — Si CI MTX, CS, photothérapie

Traitements systémiques biologiques

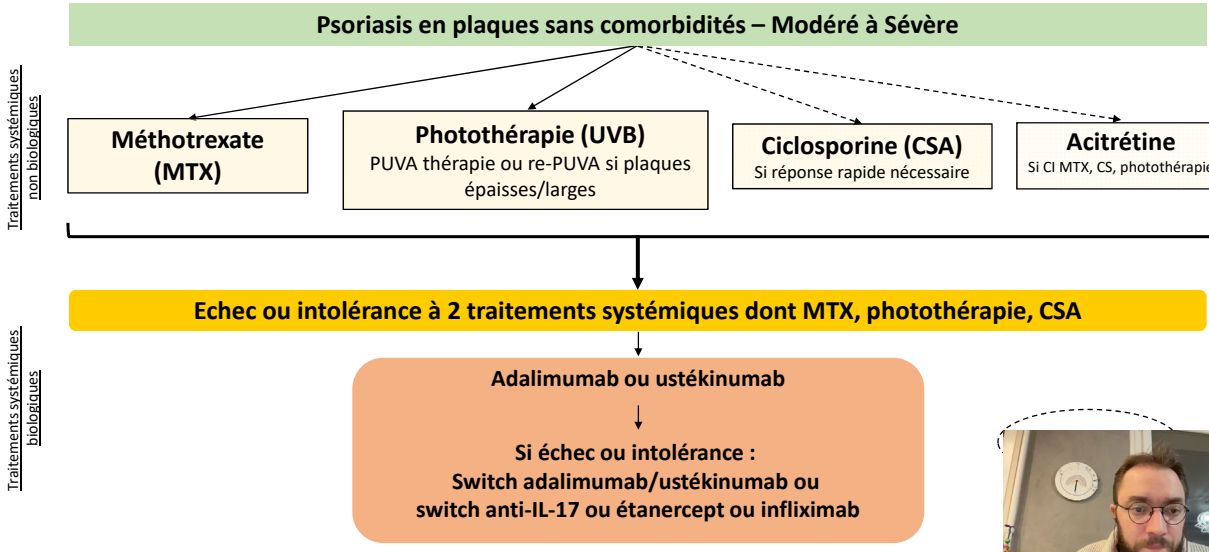
1. *Amatore F, et al. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):464-483.*
2. *Amatore F, et al. Ann Dermatol Venereol. 2019 Jun-Jul;146(6-7):429-439*

Traitements systémiques – recos Françaises 2019



1. *Amatore F, et al. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):464-483.*
2. *Amatore F, et al. Ann Dermatol Venereol. 2019 Jun-Jul;146(6-7):429-439*

Traitements systémiques – recos Françaises 2019



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2. *Amatore F, et al. Ann Dermatol Venereol. 2019 Jun-Jul;146(6-7):429-439*

Traitements systémiques – recos Europe 2020

Psoriasis en plaques sans comorbidités – Modéré à Sévère

Traitements systémiques non biologiques

- **Methotrexate (MTX)**
- ~~**Photothérapie (UVB)**~~ ~~PUVA thérapie ou re-PUVA si plaques épaisses/larges~~
  - Fumarates (non disponibles France)
- **Ciclosporine (CSA)** Si réponse rapide nécessaire
- **Acitrétine** Si CI MTX, CS, photothérapie

Traitements systémiques biologiques

1. *Nast A, et al. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498.*

Traitements systémiques – recos Europe 2020

Psoriasis en plaques sans comorbidités – Modéré à Sévère

Traitements systémiques non biologiques

- **Methotrexate (MTX)**
- ~~**Photothérapie (UVB)**~~ ~~PUVA thérapie ou re-PUVA si plaques épaisses/larges~~
  - Fumarates (non disponibles France)
- **Ciclosporine (CSA)**
- **Acitrétine**

Traitements systémiques biologiques

Echec ou intolérance 1 TTT — **France = HORS AMM**

1ère intention
- **Anti-TNFα : Adalimumab (ADA), Certolizumab (CZP)**
- **Anti-IL17 : Sécukinumab, Ixekizumab, Brodalumab**
- **Anti-IL23 : Guselkumab, Tildrakizumab, Risankizumab**

2ème intention
- **Si échec ou intolérance : Ustékinumab, Infliximab, Etanercept, Aprémilas**

1. *Nast A, et al. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498.*

Traitements systémiques – recos Europe 2020

HORS AMM

Psoriasis en plaques sans comorbidités
Atteinte sévère + échec probable des traitements systémiques non biologiques

Traitements systémiques non biologiques

Traitements systémiques biologiques

1ère intention

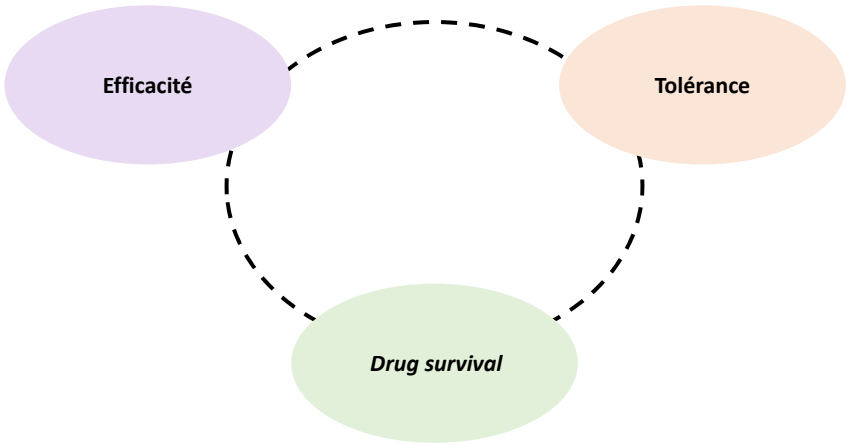
Anti-TNFα : Adalimumab (ADA), Certolizumab (CZP)
Anti-IL17 : Sécukinumab, Ixekizumab, Brodalumab
Anti-IL23 : Guselkumab, Tildrakizumab, Risankizumab

2ème intention

Si échec ou intolérance : Ustékinumab, Infliximab, Etanercept, Aprémilas

1. *Nast A, et al. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498.*

Choix thérapeutique – biothérapie 1ère ligne



Drug survival – maintien thérapeutique sous traitement

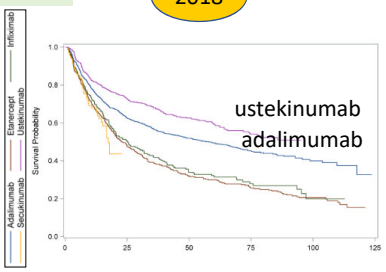
Egeberg et al., Br J Dermatol, 2018
Menter et al., JEADV, 2018
Dapavo et al. J Dermatol Treat. 2021
Torres T et al. Am J Clin Dermatol. 2021

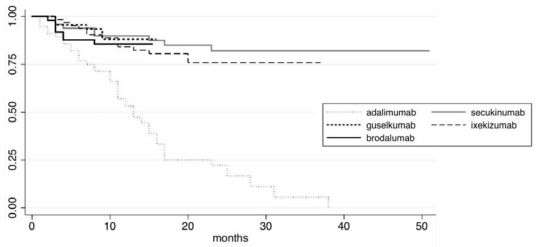
DERMBIO

2018

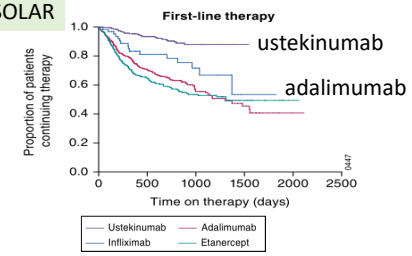
Toutes causes d'arrêt confondues

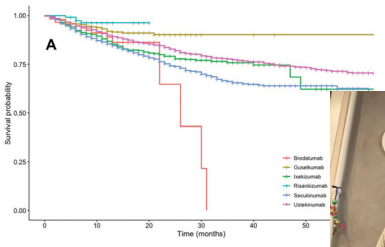
2021





PSOLAR



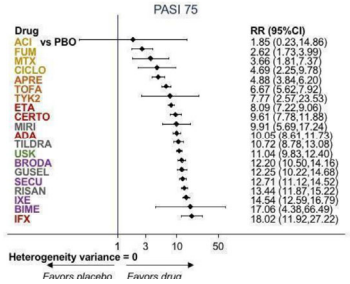


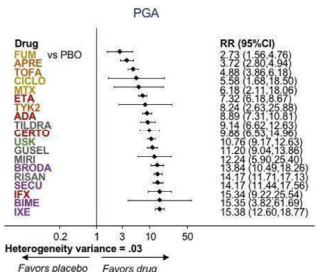
Méta-analyse en réseau – synthèse efficacité/tolérance

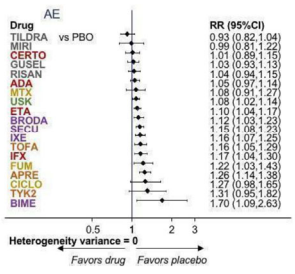
Cochrane Library
Cochrane Database of Systematic Reviews

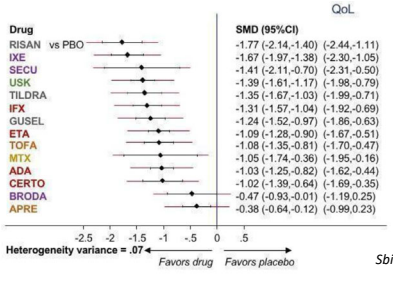
Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)

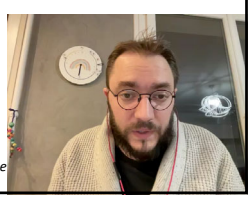
Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, Hughes C, Naldi L, Afach S, Le Cleach L











Sbidian e

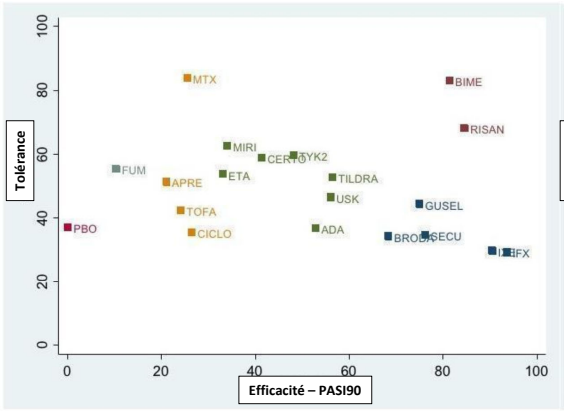
Méta-analyse en réseau – synthèse efficacité/tolérance

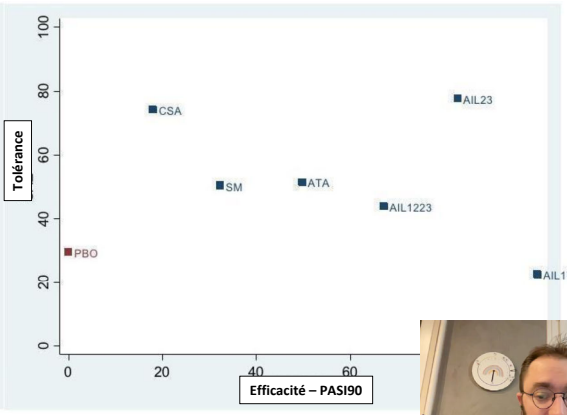
Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)

Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, Hughes C, Naldi L, Afach S, Le Cleach L

Cochrane Library

Cochrane Database of Systematic Reviews





Sbidian e

Biosimilaires

- Biosimilaires d'infliximab, étanercept et adalimumab

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
L'Assurance Maladie
Caisse Nationale
MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ
MINISTÈRE DE L'ACTION ET DES COMPTES PUBLICS

- Instructions du DGOS août 2017 :
  - Switch pour un biosimilaire = obligation d'information du patient
  - « *il convient d'encourager de façon systématique la prescription d'un médicament biosimilaire pour les initiations de traitement et pour les changements de prescription* »

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Arrêté du 3 août 2018 relatif à l'expérimentation pour l'incitation à la prescription hospitalière de médicaments biologiques similaires délivrés en ville

NOR : SSAS1821431A

- Arrêté du 3 août 2018
  - Incitation à la prescription de biosimilaires délivrés en ville
  - Reversement de 20 à 30% de la différence de prix entre princeps et biosimilaire

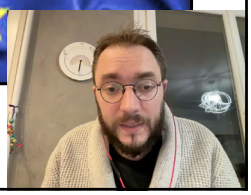
Quand réévaluer un traitement ?

Recos France

- Entre 12 et 16 semaines selon la molécule choisie
- 28 semaines pour l'Ustékinumab

Recos Europe

- 16 semaines pour les biothérapies (hors étanercept)
- 24 semaines pour les autres systémiques + étanercept



Quels sont les objectifs ?

Recos France

- PGA 0-1
- PASI90 – PASI100
- PASI absolu ≤3
- Ou
- PGA=2 ou PASI75 + DLQI<5

Recos Europe

- PGA 0-1
- PASI90 – PASI100
- PASI absolu≤2

Que faire en cas de comorbidités ? France vs Europe

- Globalement similaire pour le **rhumatisme psoriasique**

- **<u>Maladies inflammatoires chroniques de l'intestin :</u>**
  - **France** : 1 MTX; CSA or NUVB / 2 : ADA, IFX, USTK
  - **Europe** : 1 ADA, IFX, CZP, USTK / 2 anti-IL-23 (RISAN/GUSEL) / 3 MTX (Crohn) ou CSA (RCH) / 4 ACITR en association

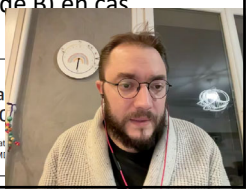
- **<u>Néoplasie</u>** :
  - France : MTX / UVB / ACITR / biothérapie au cas par cas (USTK ou anti-TNFα)
  - Europe : UVB / ACITR; 2 MTX; 3 aprémilast / biothérapie au cas par cas (anti-TNFα, USTK, anti-IL17ou anti-IL23)

- **<u>Risque cardiovasculaire majeur :</u>**
  - France : Préférer anti-TNFα (grade A) - Envisager USTK (grade A) ou anti-IL17 (grade B) en cas d'échec des anti-TNFα et contrôle des facteurs de risque
  - Europe : pas de hiérarchisation spécifique

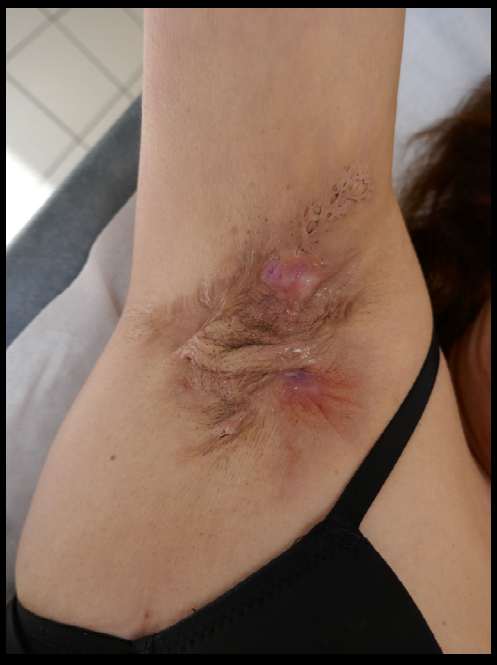

JAMA Dermatology | Original Investigation

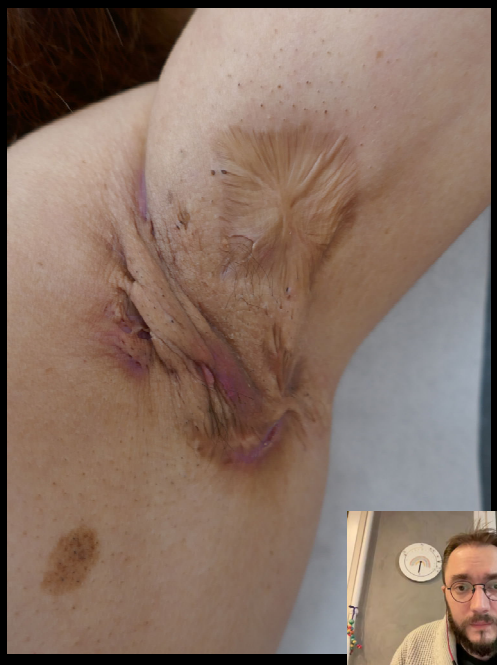
Association Between Early Severe Cardiovascula
of Treatment With the Anti–Interleukin 12/23p4

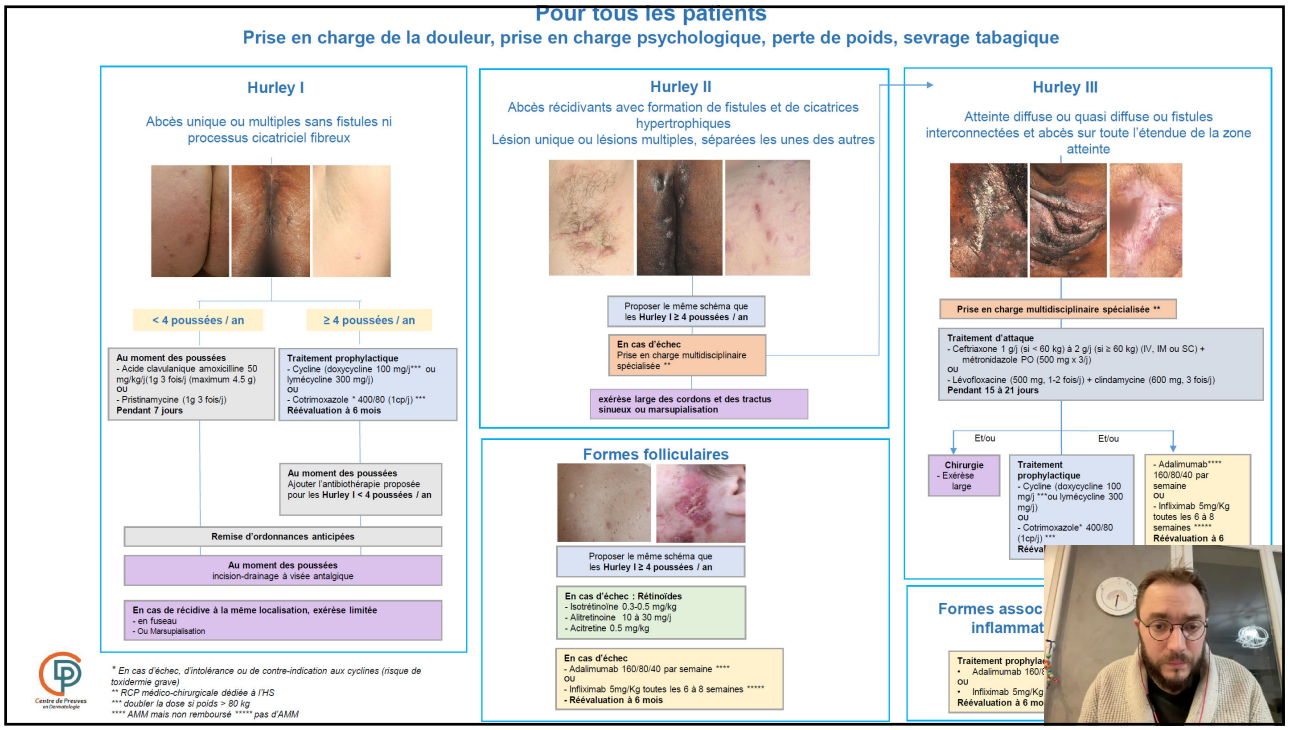
Florence Poizeau, MD; Emmanuel Nowak, PhD; Sandrine Kerbrat, MS; Béranger Le Nautout, MS; Cat
Milou-Daniel Drici, MD, PhD; Emilie Sbidian, MD, PhD; Bernard Guillot, MD, PhD; Hervé Bachelez, M
Hafid Ait-Oufella, MD, PhD; André Happe, PhD; Emmanuel Oger, MD, PhD; Alain Dupuy, MD, PhD



Hidradénite suppurée

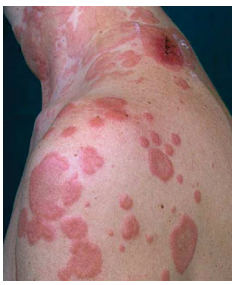


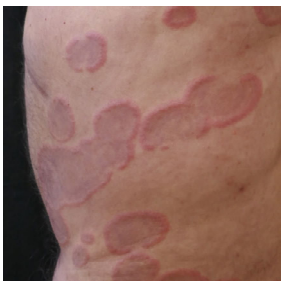


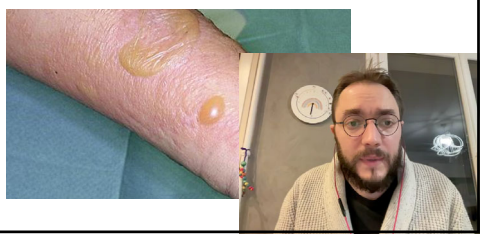


Cellulite à éosinophiles

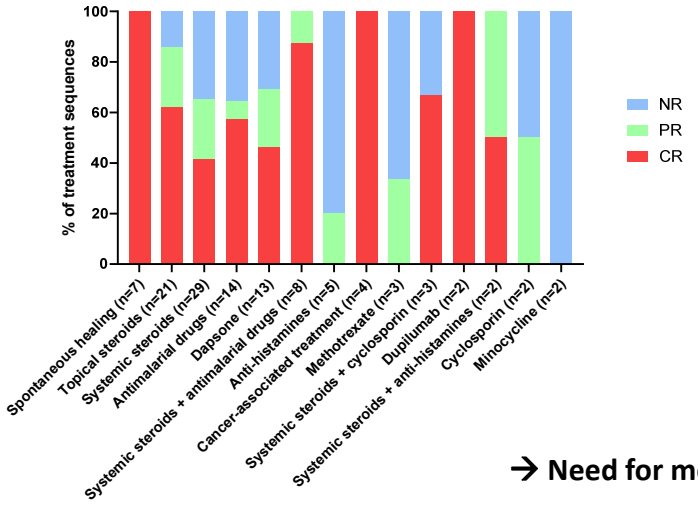
- Wide spectrum - Eosinophil infiltration (dermis+++)
- Recurrent painful or pruritic edematous plaques
- Eosinophilic cellulitis:
  - Wells syndrome: deep dermal infiltrate, pruritus/pain, edema ++
  - Eosinophilic Annular Erythema: superficial dermal infiltrate, pruritus
- Conventional treatments: topical steroids, anti-histamines, systemic steroids, disulone, hydroxychloroquine, methotrexate







Cellulite à éosinophiles



- 18 nouveaux patients
- Revue de la littérature
- Séquences thérapeutiques

- NR : non responders
- PR : partial responders
- CR : complete response

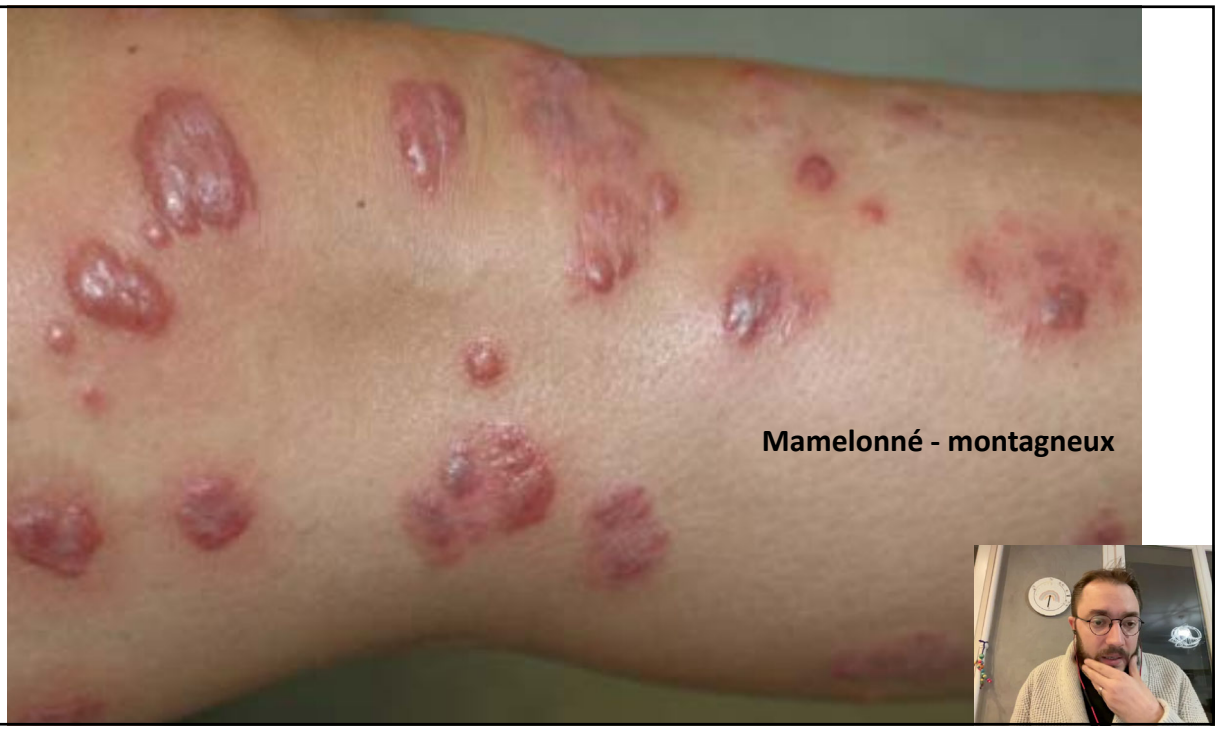
→ **Need for more specific therap**

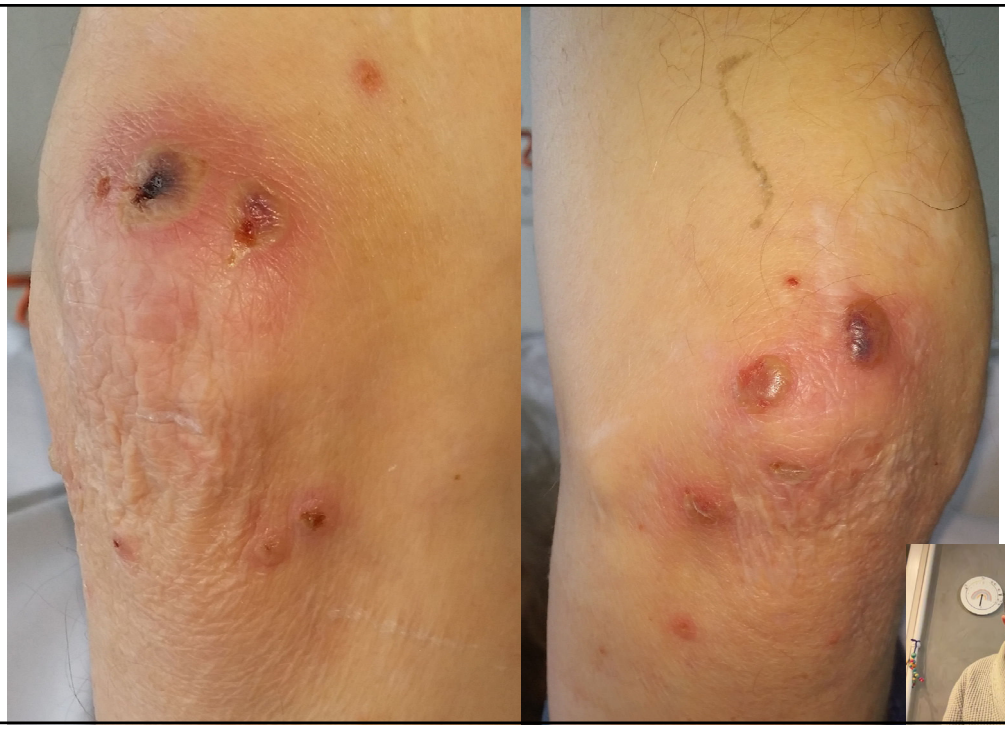
Thèse d'exercice Marine Chastagner

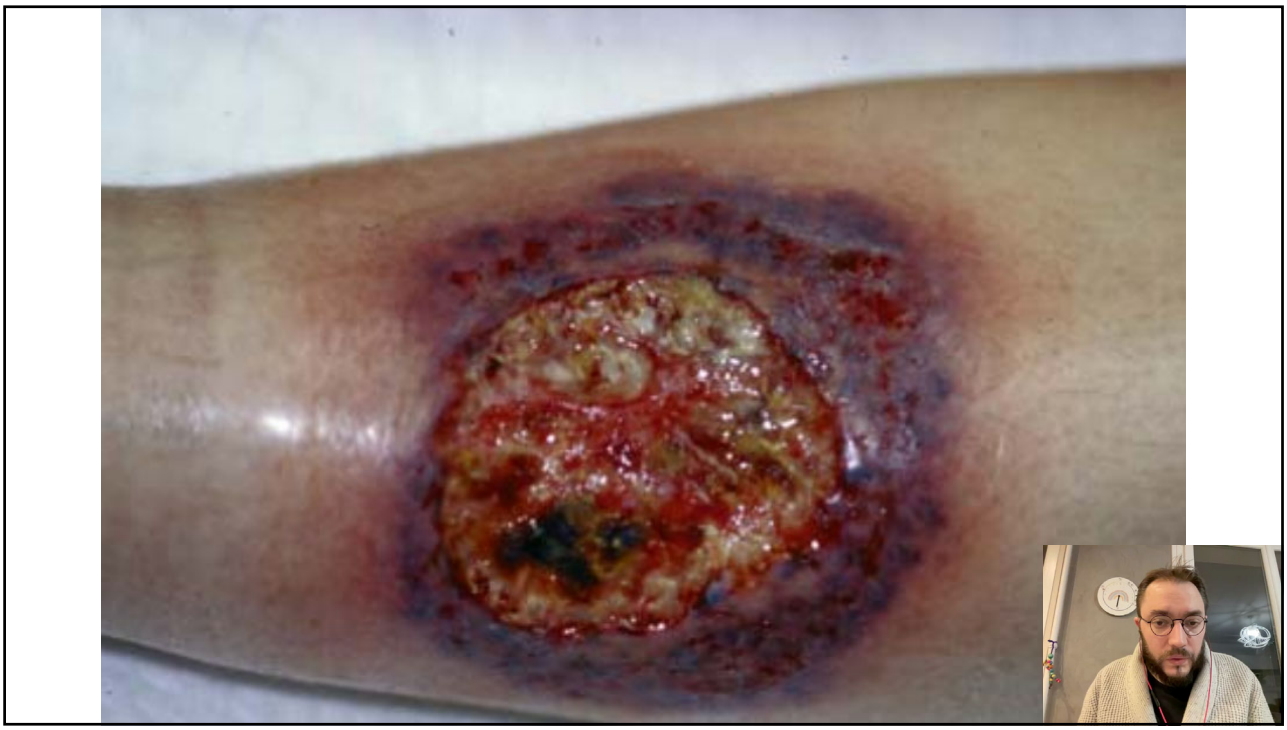
Les dermatoses neutrophiliques

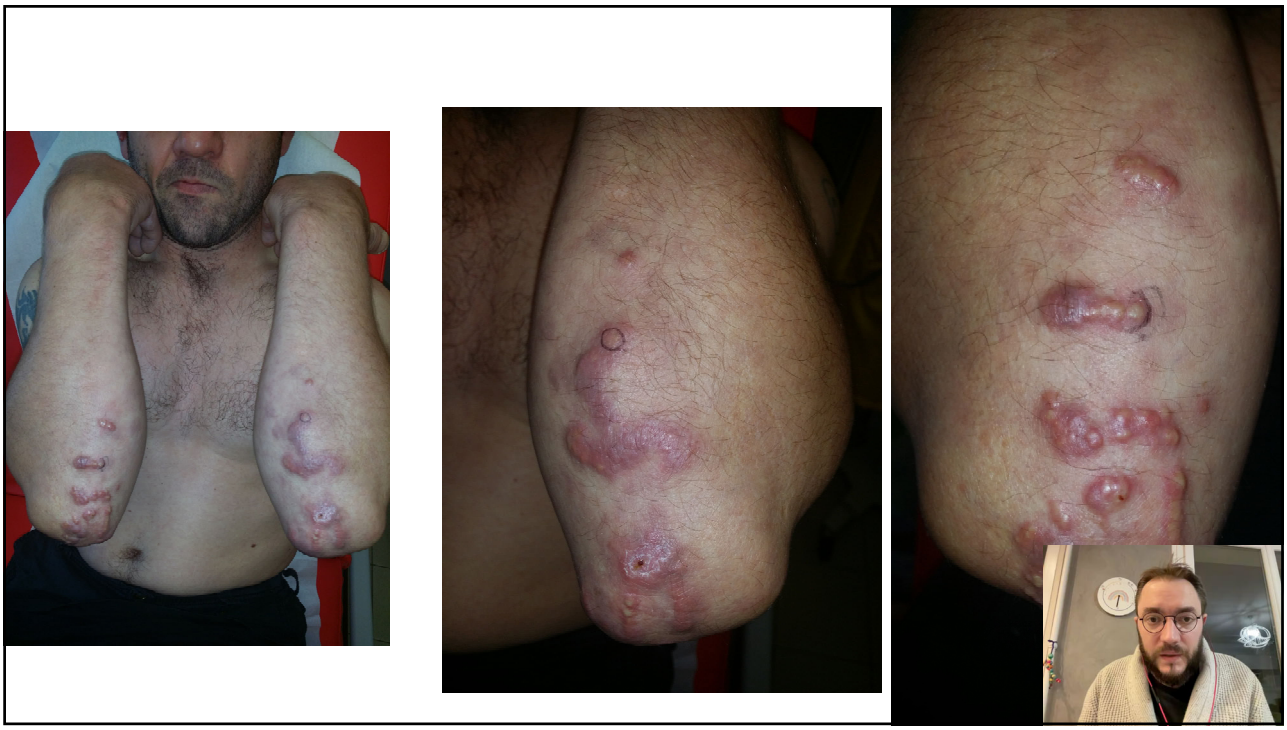
- Groupe hétérogène (moins que les Deo…)
- Historiquement « Dermatose **<u>neutrophilique</u>** **<u>aiguë</u>** **<u>fébrile</u>** » - Sweet – 1964
- Puis regroupement progressif sous la même bannière (parfois discutable) des formes suivantes :
  - Syndrome de Sweet (SyS)
  - Pyoderma gangrenosum (PG)
  - Urticaire neutrophilique (UN)
  - Pustulose amicrobienne des plis (PAP)
  - Syndrome de Sneddon-Wilkinson (SSW)
  - *Erythema elevatum diutinum* (EED)
  - DN associées aux MAI, IBDs, panniculite neutrophilique, …
  - PAPA, PASH, PSAPASH, …
  - Hidradénite eccrine neutrophile (HEN)

- Formes de chevauchement
- Association fréquente à des affections systémiques
- Atteintes extracutanées viscérales
- Sensibilité à la corticothérapie et disulone


Mamelonné - montagneux







Traitements des dermatoses neutrophiliques

- Corticothérapie systémique 0.5 – 1mg/kg diminution progressive de 10mg toutes les 4-6 semaines
- Alternatives ou corticodépendance : colchicine, disulone, immunosuppresseurs MMF, ciclosporine, tacrolimus, azathioprine

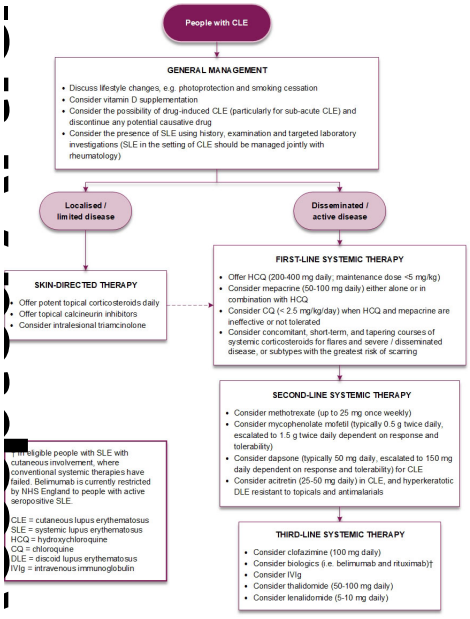
- Dans les formes sévères, chroniques :
  - Anti-TNFalpha ++++++++++++++++
  - Ustékinumab
  - Anti-IL-1

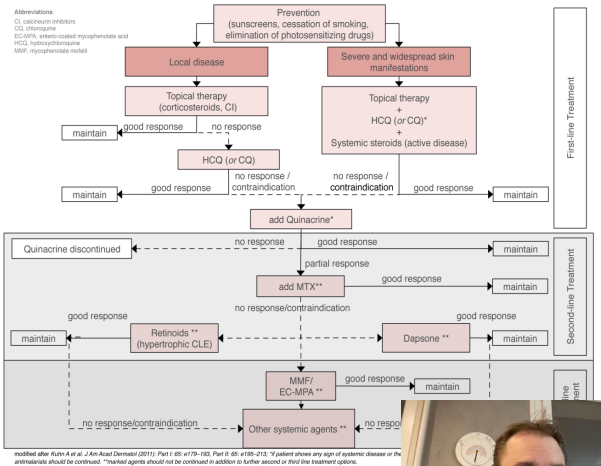
  - Anti-IL-17

  - JAKinhibitors : case reports pour le tofacitinib

- Adapter le traitement aux pathologies associées : ttt anticancéreux, attention aux MICI et

Lupus erythémateux cutané





Conclusions

- Nombreux traitements systémiques
- Ere des biothérapies

- Balance bénéfices-risques
- Comorbidités
- Modèle du psoriasis
  - Exportable ?

- Études face/face difficiles voire impossibles dans les dermatoses inflammatoires plus rares

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Merci de votre attention !