Working with the new biologicals for skin disease

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Disclaimers

- Industry
  - Advisory/Teaching/Education/Travel Honorariums
    - Janssen Cilag
    - Eli Lilly
    - Novartis
    - MSD
    - AbbVie
    - Sanofi
    - Pfizer
    - Leo Pharma
    - Amgen
    - Biogen
- Research
  - Metabolic risk in paediatric and adult psoriasis patients = No industry
  - Pharma sponsored clinical trials
    - MSD
    - UCB
    - Novartis
    - Abbvie

Disclaimer

- I will be talking about medications that may not currently be TGA approved of listed on PBS.
- For the conditions discussed, the medications that are on the PBS are for prescription by a dermatologist +/- immunologist.
- Please no photography of clinical photos.
  - Patients have consented to their use for me to use in education only.

Objectives

- Overview of main medical dermatological conditions that can be managed with biologic agents
- An understanding of the disease specific qualification pathways for access to the various biological agents
- A brief understanding of the mode of action of the biologic agents in the disease(s) in which they are used.
- An understanding of the important facets of the work up and monitoring process for each medication
- An understanding of the key and important adverse reactions

Introduction

- Psoriasis
- Chronic Spontaneous Urticaria
- Hidradenitis Suppurativa
- Atopic Dermatitis

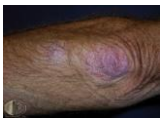
Psoriasis

Psoriasis Is a Chronic, Debilitating Skin Disease that affects millions worldwide[2]

- Affects 2–7% of Australians,[1]
- Almost twice as common in Australian men as in women[1]
- Causes considerable psychosocial disability and has a major impact on a patients QoL[1]

Characterized by red, scaly plaques that vary in severity from localized areas to complete body coverage[1,2]

Manifestations of psoriasis include functional limiting sites such as palms and soles, scalp, nails, genital regions and body folds[3]

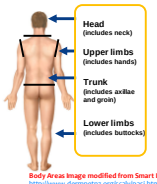


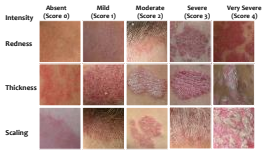
1. Parisi R, et al. *J Invest Dermatol*. 2013;133:377–85. 2. Johnson-Huang LM, et al. *Dis Model Mech*. 2012;5:423–33.
3. Baker C, et al. Australas *J Dermatol*. 2013;54:148–54.
Pictures: http://www.dermnetnz.org/scaly/img/plaque-psoriasis/index.html. Accessed 19/05/15

Psoriasis Area and Severity Index (PASI) Calculation[1]

- Plaques are graded based on 3 criteria: redness (R), thickness (T), and scaliness (S)
- Severity is rated for each index on a 0-4 scale (0 for no involvement; 4 for severe involvement).
- The body is divided into 4 regions: head (h), upper extremities (u), trunk (t), and lower extremities (l). In each of these areas, the fraction of total surface area affected is graded on a 0 to 6 scale (0, no involvement; up to 6 for >90 % involvement).
- The various body regions are weighted to reflect their respective proportion of body surface area. The composite PASI score can then be calculated:

$$PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$$





Body Areas Image modified from Smart Image database from Novartis Global . Grading of psoriatic plaques images : http://www.dermnetnz.org/scaly/pasi.html. Accessed 19/05/15. Reference 1 : Naldi,L. Clinics in Dermatology (2010) 28, 67–72.

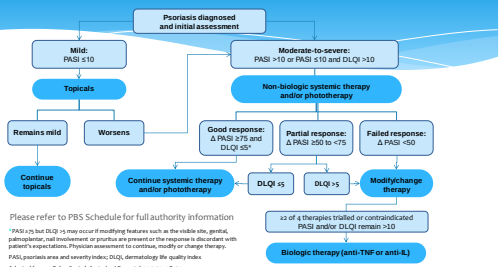
IGA mod 2011 Rating Scale for Overall Psoriatic Disease- one of many assessment tools[1]

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions

Table adapted from Langley RG, et al. *J Dermatolog Treat*. 2015 Feb;26(1):23-31

1. Langley RG, et al. *J Dermatolog Treat*. 2015 Feb;26(1):23-31

Treatment Algorithm for Australian Patients With Psoriasis[1]



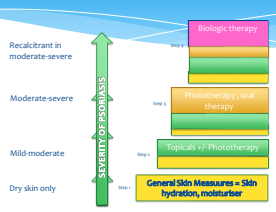
*PASI ≤75 but DLQI >5 may occur if modifying features such as the visible site, genital, palmoplantar, nail involvement or pruritus are present or the response is discordant with patient's expectations. Physician assessment to continue, modify or change therapy.

PASI, psoriasis area and severity index; DLQI, dermatology life quality index

Adapted from: 1. Baker C, et al. Australas *J Dermatol*. 2013;54:148–54.

Lay of the land - Current

- Moisturiser: "basic step"
- Topical:
  - Corticosteroids
  - VitD3 analogues
  - LPC;SalAcid
  - Dithranol
  - Retinoids
- Phototherapy:
  - NBUVB, PUVA
- Systemic:
  - Neotigasone
  - Methotrexate
  - Cyclosporine
  - *Fumaric Acids
  - *Apremilast
- Biologic agents:
  - See next slide



Biologic Therapies Available in Australia for the Treatment of Moderate to Severe Plaque Psoriasis

Generic Name (Brand Name)	Class	Target	Molecular Structure	Sponsor/ Company
Etanercept (Enbrel™) Biosimilar: Brenzys™; *Erelzi™	TNF-a inhibitor	TNF-a	Receptor fusion protein	Pfizer Merk Sharpe Dohme/Samsung; Sandoz
Infliximab (Remicade™) Biosimilar: Inflectra™; Renflexis™	TNF-a inhibitor	TNF-a	Chimeric monoclonal antibody	Janssen Cilag Pfizer; Merk Sharpe Dohme
Adalimumab (Humira™) Biosimilar: *Amgevita™	TNF-a inhibitor	TNF-a	Fully human monoclonal antibody	AbbVie Amgen
Ustekinumab (Stelara™)	IL-12/23 inhibitor	p40 subunit	Fully human monoclonal antibody	Janssen Cilag
Secukinumab (Cosentyx™)	IL-17A inhibitor	IL-17A	Fully human monoclonal antibody	Novartis
Ixekizumab (Taltz™)	IL-17A antagonist	IL-17A	Humanised Monoclonal antibody	Eli Lilly
***Guselkimab (Tremfya™)**	IL-23 inhibitor	IL-23 p19 subunit	*Fully Human Monoclonal antibody*	*Janssen*
***Risankizumab (?™)**	*IL-23 inhibitor*	IL-23 p19 subunit	*Humanised Monoclonal antibody*	*AbbVie*

Prior to prescription

- Chronic moderate to severe psoriasis PASI >=15 or H&F/Face >30%BSA
- Fail/adverse reaction/contraindicated to 3 of 4 systemic treatments
  - NBUVB
  - Acitretin
  - Methotrexate
  - Cyclosporine
- Biologic work up
  - Immunisation status:
    - Measles/Mumps/Rubella/Varicella
    - Hep A/B/C and HIV
    - ANA
    - Metabolic screening
  - Quantiferon Gold Tb™
  - ?Strongyloides serology (Tends to be geographic specific based on risk)
  - Age appropriate tumour markers and associated investigations

On treatment

- Some variation between practices
- Typically
  - 3monthly: FBC/EUC/LFT/CRP/ESR
  - 6monthly: FSE and lymph nodes
  - 12monthly: Quantiferon Gold Tb™/Metabolic screen
- Adhoc
  - Based on symptoms and exposure risks

Common and Important adverse effects

- Common
  - URTI
    - Nasopharyngitis/Rhinitis
  - Candidiasis
    - Mucosal: Oral/Genital
    - Cutaneous
  - Injection site reactions
  - Urticaria
- Important
  - Neutropenia
  - Drug induced Lupus – Mainly seen in TNFa
  - IBD flares/onset with IL-17's
  - Hypersensitivity reactions
  - Live vaccines
- *Pregnancy

Moderate to Severe Chronic Plaque Psoriasis

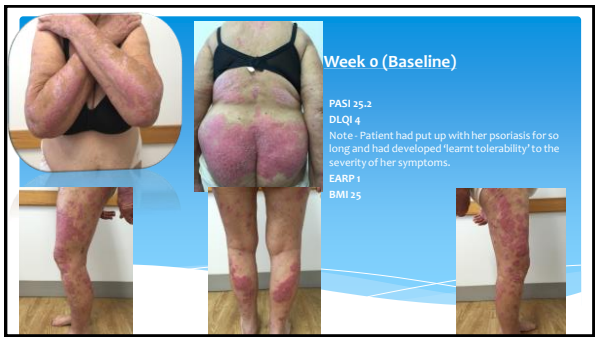
Biologic Naïve Patient
Commenced on seckinumab

Patient History

- 78y.o. female
- 25year history of chronic plaque psoriasis
- Comorbidities
  - Ischaemic heart disease (coronary artery stent 2013)
  - Osteoporosis
  - Chronic 'Arthritis'
- Medications
  - Betaloc 50mg daily
  - Calcium/Cholecalciferol 600mg/200IU daily
  - Cartia 100mg daily
  - Lipitor 60mg daily

Systemic management of her psoriasis

- Patient tended to have a response to initial medications/treatments for her chronic plaque psoriasis. However, the treatments would lose effectiveness
- Treatments trialled:
  - Phototherapy – Narrow Band UVB 3x weekly
  - Acitretin 25mg daily
  - Methotrexate 10-15mg weekly
  - Apremilast 30mg BD


Week 0 (Baseline)
PASI 25.2
DLQI 4
Note - Patient had put up with her psoriasis for so long and had developed 'learnt tolerability' to the severity of her symptoms.
EARP 1
BMI 25


Week 1 (7days after first injection of seckinumab)
PASI 20.1
DLQI 4
EARP 1


Week 2 (14days after first injection of seckinumab)
PASI 13.4
DLQI 1
EARP 1


Week 3 (21 days after first injection of seckinumab)
PASI 9.8
DLQI 1
EARP 0


Week 4 (28days after first seckinumab injection)
PASI 5.3
DLQI 1
EARP 0


Week 8 (56days after first injection of seckinumab)
PASI 1.2
Note mainly post inflammatory pigment changes.
DLQI 0
EARP 0

Understanding Biosimilars

- Jumbo jet and the matchbox car
  - Unlike generic medicines in which the active ingredients are identical to the reference small–molecule drug, biosimilars will not be identical to the reference biologics
  - Due to processes associated with translating biologics from living cells in the laboratory to mass-production molecules, biosimilars can only be highly similar to the reference product they are designed to resemble; there is no way to make identical copies of biologics
    - 150Daltons versus 150,000Daltons
- Postmarketing safety issues for biosimilars is essential
- Cost considerations for use of biosimilars and physician choice
  - In 2015 the PBAC advised that biosimilar products would be suitable for substitution at the pharmacy level, where the data support this conclusion

British Journal of Dermatology (2017) 177, pp1495–1502

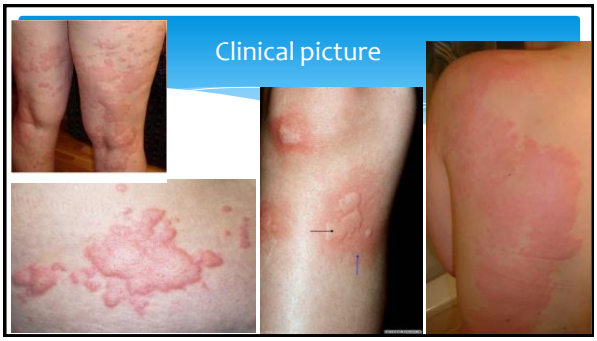
Chronic Spontaneous Urticaria

Overview

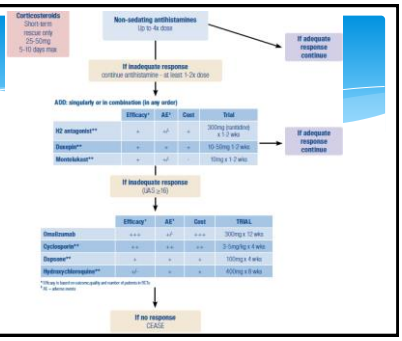
- Chronic spontaneous urticaria (CSU), AKA chronic idiopathic urticaria.
- It is characterised by itchy wheals (hives) which arise spontaneously for at least 6 weeks, with or without angioedema, and that have no apparent external trigger.
  - The wheals are typically characterised by three features:
    - swelling and erythema;
    - an itching or burning sensation; and
    - a transient nature, with the skin returning to normal within 1–24 hours.
- Angioedema is characterised by:
  - A sudden, pronounced erythematous or skin-coloured swelling of the lower dermis and subcutis;
  - Frequent involvement below mucous membranes;
  - Sometimes pain rather than itching; and
  - A longer time to resolve than the wheals (up to 72 hours).
- CSU differs from the inducible (physical) urticarias, where lesions are induced by physical stimuli such as scratching (dermographism), cold (cold urticaria), sunlight (solar urticaria), increased body heat (cholinergic urticaria), pressure (delayed pressure urticaria) or vibration.

Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69(7):868-887.

Clinical picture



ASCIA Guidelines - Chronic Spontaneous Urticaria (CSU) 2015



Biologic

Generic Name (Brand Name)	Class	Target	Molecular Structure	Sponsor/ Company
Omalizumab (Xolair™)	IgE Inhibitor	IgE	Humanised IgE Fc Region antibody	Pfizer Merk Sharpe Dohme/Samsung; Sandoz

Prior to Treatment

- Failed/adverse reaction/contraindication increased dosing of antihistamines
- And, failed one of:
  - Ranitidine 300mg daily
  - Doxepin 10mg daily
  - Leukotriene inhibitor
- Urticaria Activity 7 (UAS7) score >=16
  - Daily number of Urticaria wheals (0 = mild to 3 = intense scale)
  - Daily intensity of Itch (0 = mild to 3 = intense scale)
- No specific work up
  - However, will have been screen for many potential triggers CSU prior to prescription

During Treatment

- 300mg every 4 weeks for 12weeks then review
- Day of injection
  - Observe for 2hours

Main side effects

- Injection site reactions (45%)
- colds (23%)
- sinus infections (16%)
- headache (15%)
- sore throat (11%)
- The rate of these was not dissimilar to placebo

https://www.xolairhcp.com/starting-treatment.html

Key and important adverse effects

- The main adverse effect is anaphylaxis[1]
  - Rate of occurrence of 1 to 2 patients per 1,000
  - The allergic reaction is probably not due to the binding characteristics of the antibody drug, but to the protein nature of the antibody
- Small increase in the risk of strokes and heart disease[2]
- IgE may play an important role in immune system recognizing cancer cells.
  - The data suggest that a causal relationship between omalizumab therapy and malignancy is unlikely[3]

1. Fanta CH (March 2009). "Asthma". *N. Engl. J. Med.* **360** (10): 1002–14.
2. 2. "Xolair (omalizumab): Drug Safety Communication - Slightly Elevated Risk of Cardiovascular and Cerebrovascular Serious Adverse Events". fda.gov. 2014-09-26. Retrieved 29 September 2014.
3. 3. Busse W, et al (April 2011). "Omalizumab and the risk of malignancy: results from a pooled analysis". *The Journal of Allergy and Clinical Immunology*. **125** (4): 983–9.e6.

Hidradenitis Suppurativa

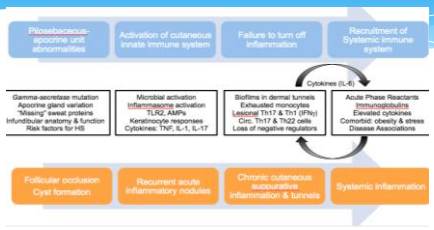
Overview

- Hidradenitis suppurativa (HS), also known as acne inversa, is a painful, chronic inflammatory skin disease.
- Characterized by
  - multifocal, recurrent nodules, abscesses, and fistulas, predominantly affecting the axillary, inguinal, breast-fold, and anogenital regions
- Women are affected 2 to 5 times as frequently as men.
- More common in smokers

Prevalence

- worldwide data indicate the prevalence of HS to be between 0.05 to 4%
- Australian population ~ 23 million (2013)
  - 2% of Australian population
  - (similar to psoriasis)
  - Estimated: 460, 000
- USA: orphan disease National Organization for Rare Diseases (NORD)
  - prevalence (number of total cases at a given point in time) of less than 200,000 cases in the US '
- HUGE unmet need

Pathophysiology



Classifying disease

- Phenotypes - patterns of disease
- Photography – change in disease/ inflammation
- Ultrasound – identification of tunnels
- **Hurley Staging system**

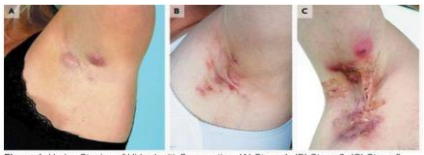
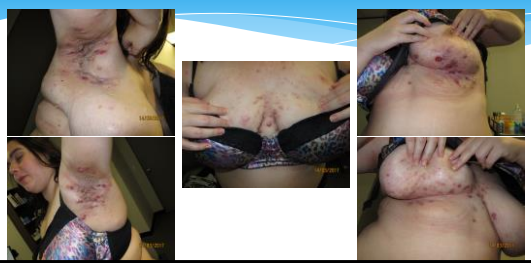


Figure 1. Hurley Staging of HidradenitisSuppurativa (A) Stage 1, (B) Stage 2, (C) Stage 3. From: Jemec, NEJM, 2012[2].



Management

- Working on Australian Consensus Guidelines
- Modification of key patient factors
  - Quit smoking/Lose weight
- Antibiotics
  - Mino/Doxy/Rif+Clinda
- Hormonal therapy
  - Spiranolactone/Metformin/OCP/Finasteride
- **Biologic**
  - **Adalimumab (Humira) – PBS listed**
  - **In trial = IL17, IL-23**
- Surgery

Biologics

Generic Name (Brand Name)	Class	Target	Molecular Structure	Sponsor/ Company
Adalimumab (Humira®)	TNF-a inhibitor	TNF-a	Fully human monoclonal antibody	AbbVie
***Infliximab (Remicade®)**	TNF-a inhibitor	TNF-a	Chimeric monoclonal antibody	Janssen Cilag
***Ustekinumab (Stelara®)**	IL-12/23 inhibitor	p40 subunit	Fully human monoclonal antibody	Janssen Cilag
****Secukinumab (Cosentyx®)**	IL-17A inhibitor	IL-17A	Fully human monoclonal antibody	Novartis
****Bimekizumab**	IL-17A antagonist	IL-17A and IL17F	Monoclonal antibody	UCB

Prior to treatment

- Hurley stage II/III
- Fail/adverse reaction/contraindicated to 2 oral antibiotics for 3months each
- Biologic work up
  - Immunisation status:
    - Measles/Mumps/Rubella/Varicella
    - Hep A/B/C and HIV
    - ANA
    - Metabolic screening
  - Quantiferon Gold Tb^{TM}
  - ?Strongyloides serology (Tends to be geographic specific based on risk)
  - Age appropriate tumour markers and associated investigations

On treatment

- Some variation between practices
  - Still being defined in many ways
- Typically
  - 3monthly: FBC/EUC/LFT/CRP/ESR
  - 6monthly: FSE and lymph nodes
  - 12monthly: Quantiferon Gold Tb^{TM}/Metabolic screen
- Adhoc
  - Based on symptoms and exposure risks

Common and Important adverse effects

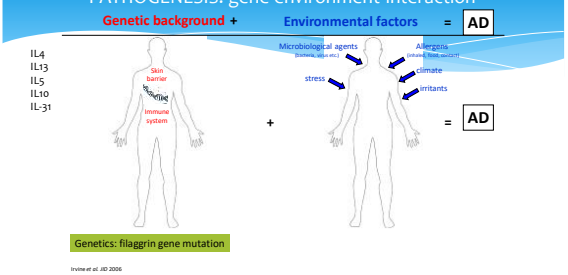
- Common
  - URTI
    - Nasopharyngitis/Rhinitis
  - Candidiasis
    - Mucosal: Oral/Genital
    - Cutaneous
  - Injection site reactions
  - Urticaria
- Important
  - Neutropenia
  - Drug induced Lupus – Mainly seen in TNFa
  - IBD flares/onset with IL-17's
  - Hypersensitivity reactions
  - Live vaccines
- *Pregnancy

Atopic Dermatitis

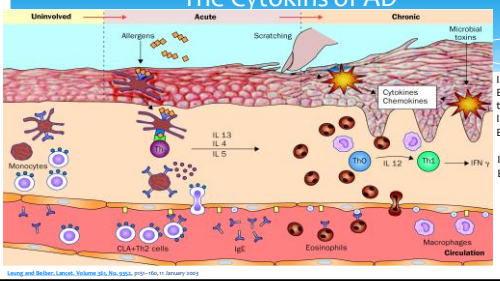
Overview of AD

- Atopic dermatitis (AD) is chronic inflammatory skin condition
- Characterized by
  - skin barrier defects,
  - T helper type 2 cell activation, and
  - increased risk for cutaneous and extracutaneous infections.

PATHOGENESIS: gene-environment interaction



The Cytokins of AD



IL4/IL13
Epidermal thickening
Inflammation
Elevates IgE

IL5
Eosinophilia

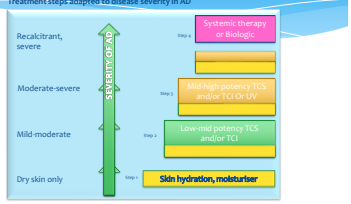
IL31
Pruritus
Inflammation

Leung and Bieber, Lancet, Volume 361, No. 9352, 960–160, 11 January 2003

Management: The therapeutic ladder

- Moisturiser: "basic step"
- Topicals: limited options
  - Corticosteroids, TCI
- Phototherapy:
  - UV A and B
- Systemics: Many often off-label
  - Immunosuppression: CSA, MTX, AZA, MMF
  - Systemic corticosteroids
  - Biological: Dupilumab (TGA approved but not PBS); Nemoluzumab (Trial).
  - Jak/Stat/Tyk2 (various molecules and trials)
- Others:
  - Anti-histamines target itch
  - Lifestyle approaches
  - Trigger avoidance
  - Psychotherapy

Treatment steps adapted to disease severity in AD



Adapted from Akdis et al. Allergy 2006

Biologic Therapies for the Treatment of Moderate to Severe Adult atopic dermatitis

Generic Name (Brand Name)	Class	Target	Molecular Structure	Sponsor/ Company
Dupilumab (Dupixent®)	IL4/IL13	IL4/IL13	Fully human monoclonal antibody	Sanofi Genzyme
***Nemoluzumab (?®)**	IL-31	IL-31	Fully humanised Monoclonal antibody	Galderma
***Lebrikizumab**	IL13	IL13	Fully humanized monoclonal antibody	Dermira (originally from Roche)
***Ustekinumab (Stelara®)**	IL-12/23 inhibitor	p40 subunit	Fully human monoclonal antibody	Janssen Cilag
ETC				

Prior to treatment

- At this stage we are uncertain what the possible medicare qualifying criteria will be.
  - Will involve a measurable definition of disease severity eg EASI, SCORAD
  - Likely will involve treatment with cyclosporine prior as it's the main oral systemic agent with clinical trials in AD
- Immunisation status:
  - Measles/Mumps/Rubella/Varicella
    - Need avoid live vaccines once on treatment.
    - Non-live vaccines have been examined as same as placebo and considered safe.
  - Hep A/B/C and HIV
  - ANA
  - Metabolic screening
  - ?TB screeing?

During treatment

- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week.
  - Again uncertain what the PBAC recommendation will be
- WARNINGS AND PRECAUTIONS
  - Hypersensitivity: If a systemic hypersensitivity reaction occurs, discontinue DUPIXENT immediately and initiate appropriate therapy.
  - Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider.
  - Comorbid Asthma: Advise patients with comorbid asthma not to adjust or stop their asthma treatment without consultation with their physicians.
  - Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections.

Key and important adverse effects

- Injection site reactions 10% (placebo 5%)
- Conjunctivitis 10% (placebo 2-5%)
- Blepharitis 2-5% (placebo 1%)
- Oral herpes 4% (placebo 2%)
- Keratitis <1-4% (placebo 0%)
- Eye pruritus 1-2% (placebo 1%)
- Other herpes simplex infection 2% (placebo 1%)
- Dry eye <1-2% (placebo <1%)
- Note – active n= 639, placebo n= 832

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf