Recent Advances In Therapeutics

Medical Update Group September 2019 Sadeck Vawda

Recent Advances in Therapeutics

- Immunotherapy for Cancer
  - Car T Cell Therapy
  - Immune Checkpoint Inhibitors
- New drugs in the management of migraine
- Atopic Dermatitis: A New Era
- Miscellaneous breakthroughs

Immunotherapy For Cancer

Definition: Use of body's own immune system to fight disease.

Immuno-Oncology: Specifically targeted to fight cancer

Immuno-Oncology

- Under normal circumstances, our immune system is able to destroy cancer cells in our body.

- However, cancer cells can adapt and mutate, effectively hiding from our immune system ⟶ development of tumours.

- Immuno-Oncology ⟶ mobilising lymphocytes to recognise and eliminate cancer cells using the body's immune system.

Therapies for Cancer

- Surgery
- Radiotherapy
- Chemotherapy
- Targeted therapies (e.g. transtuzumbab in breast cancer, imatinib in CML)
- Immunotherapy hailed as the 5th pillar to combat cancer

Immuno-Oncology Therapy

- Allows cancer cells to be targeted, leaving the rest of the body unharmed.
- Fewer limitations (applicable to tumours at all stages with much higher efficiency and durability).

3 Types of Immuno-Oncology Therapy

- Cellular Therapy (e.g Car T Cell Therapy)
- Immune checkpoint inhibitors + monoclonal Antibodies
- Cancer Vaccines

I. CAR T CELL THERAPY

- Engineering patients' immune cells to treat their cancers

CAR T CELL THERAPY

- Has captured the attention of researchers in small clinical trials, in patients with advanced blood cancers.
- Remarkable responses in some patients from whom all other treatment were ineffective.

CAR T CELL THERAPY

In 2017, Two Car T Therapies were approved by USFDA

- One for the treatment of children with acute lymphoblastic leukemia (ALL)
- One for the treatment of adults with advanced lymphomas.

CAR T CELL THERAPY

- Equivalent of giving patients a living drug
- Back bone of CAR T Cells is T Cells (Workhorses of the immune system. Critical role in orchestrating the immune response and killing cells infected by pathogens).

CAR T CELL THERAPY

- Therapy consists of drawing blood from patients and separating out the T cells.
- Next using a disarmed virus, the T cells are genetically engineered to produce receptors on their surface called Chimeric Antigen Receptors or CARs.
- These receptors are synthetic molecules that allow the T cells to recognize and attached to a specific protein, antigen or tumor cells
- Once the collected T cells have been engineered to express the antigen-specific CAR, they are "expanded" in the laboratory into hundreds of millions.
- The final step is the infusion of the CAR T Cells into the patients.

CAR T CELL THERAPY

- The Engineered cells further multiply in the patient's body and with guidance from their engineered receptors, recognize and kill cancer cells.
- Advances in intracellular engineering of CAR T cells have improved T cell's ability to replicate after infusion and survive longer in circulation.
- To produce a Batch of CAR T cells in the laboratory takes less than 7 days.

CAR T CELL THERAPY

- Initial development of CAR T cells therapies has focused largely on ALL, the most common cancer in children.
- More than 80% of children with ALL that arises in B cells - the predominant type of pediatric ALL – will be cured by intensive chemotherapy.
- For those who relapse after chemotherapy or stem cell transplant, treatment options are close to none.
- ALL is a leading cause of death from childhood cancer.
- In the initial trials in children with ALL not responding to existing therapies or has recurred, CAR T Cells therapy provided a complete response in 27 out of 30 patients with many patients showing no signs of recurrence long after treatment.
- Single treatment

CAR T-Cell Therapy

- These early successes laid the foundation of a CD-19 targeted Car T-Cells therapy called Tisangenlecleucel (Kymriah) for children and adolescents with ALL
- Many of the patients had complete and long lasting remissions
- Based on the trial results, FDA approved the drug in August 2017
- There are no shortage of promising data on CAR T-cells to treat adult patients with blood cancers
- Findings from a large trial has led to the approval of a second CAR T-Cell product (Axicabtagene Ciloleucel (Yescarta) in some patients with Lymphoma).

CAR T-Cell Therapy

- Results to date in Lymphomas have been incredibly successful
- CAR T-Cell are almost certain to become a frequently used therapy for several types of Lymphomas.
- Rapid advances in and growth of Car T-Cell Therapy has exceeded all expectations

CAR T-Cell Therapy

Understanding/Managing Side Effects

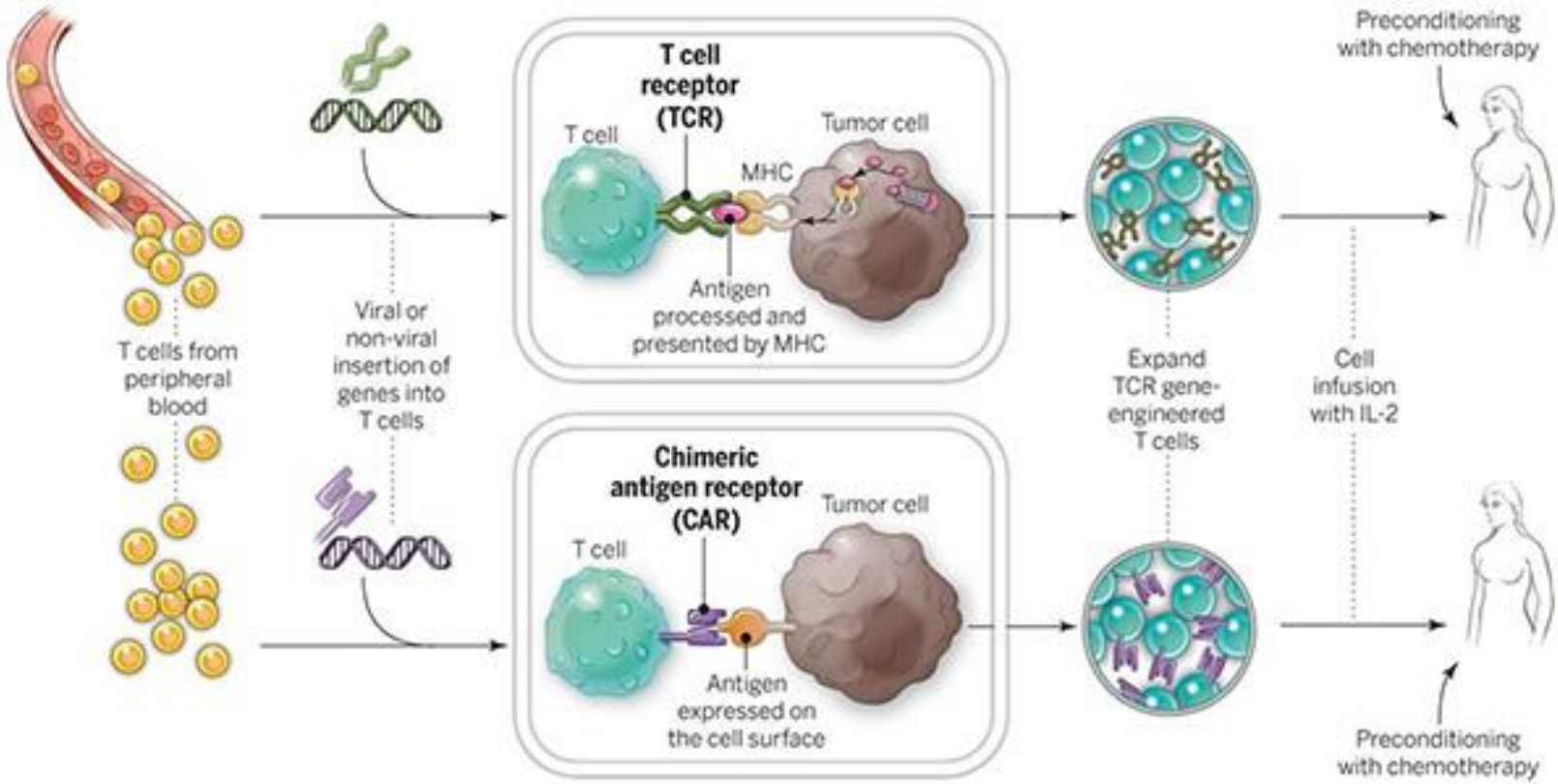
- Like all cancer therapies, CAR T-Cell therapy can cause several worrisome and sometimes fatal side effects.
- One of the most frequent is Cytokine Release Syndrome (CRS).
- Cytokines are released by T Cells as part of their immune duties to stimulate and direct the immune system.
- In CRS, there is a massive release of cytokines in the blood stream which can lead to dangerously high fever and precipitous drops in blood pressure.

CAR T-Cell Therapy

Understanding/Managing Side Effects

- CRS is managed with standard supportive therapies including steroids
- Research has shown that patients with severe CRS had particularly high levels of IL-6, a cytokine secreted by T-Cells.
- Tocilizumab (Actemra) which blocks IL-6 activity resolves the problem in most patients and has become a standard therapy for severe CRS.
- Another side effect of CAR T-Cell therapy is a mass die off of B cells (B cells aplasia). B cells are killed by CAR T-Cells. To compensate, many patients are given immunoglobulin therapy in order to have the necessary antibodies to fight infection.
- Another potentially fatal side effect is cerebral edema.

Car T cells are engineered to produce special receptors on their surfaces. They are then expanded in the lab and returned to the patient
Credit: National Cancer Institute



CAR T-Cell Therapy

The Future

- Research is continuing at a swift pace. Mostly in patients with blood cancers
- The number of trials has expanded exponentially (>180)
- Antigen targets for Car-T Cell therapy have been identified in other blood cancers including multiple myeloma.

CAR T-Cell Therapy

The Future

- Research ongoing for solid tumors as well though there is some skepticism whether it will have the same success.
- Finding suitable antigens to target on solid tumors is a challenge
- Majority of tumor antigen in solid tumors reside inside tumor cells out of reach of CAR, which can only target surface antigens.
- Another line of research is to use cells not collected from the patient but from healthy donors – "off the shelf approach"
- The future looks bright for CAR T-Cell therapy.

Monoclonal Antibodies

- Many MABs treatment has been approved in recent years

  e.g transtuzumab (Herceptin) in breast cancer
  alemtuzumab (Campath) in leukemia
  rituximab (Rituxan) in leukemia/lymphoma
  cetuximab (erbitux) in colorectal cancer

- This type of Immuno-Oncology therapy works by engineering antibodies to target tumour associated antigens.

Immune Checkpoints

- Brilliance of the immune system ⟶ tell the difference between normal and foreign/harmful cells
- Uses checkpoints to do so ⟶ Turn up or turn down a signal
- Tumours interfere with these signals to hide from immune responses.

Immunotherapy by checkpoint Inhibition

- Profoundly changing cancer therapy
- Number of indications growing at an unprecedented rate
- Both in solid tumours/haematologic malignancies
- Urgent need for better standardized biomarkers

Immune Checkpoint Inhibition

- Immune checkpoint inhibitor treatment involves antibodies generated against cytotoxic T-Lymphocyte associated:

  Protein 4 (CTLA-4)

  Programmed death receptor 1 (PD-1) or its

  Ligand (PD-LI)

- These checkpoint proteins stop T-Cells from attacking other cells
- In Cancer, abundance of these check point proteins ⟶ Allow them to evade the immune system.
- Inhibition of these checkpoints proteins ⟶ Boost immune system to kill cancer cells

Immune Checkpoint Inhibitors used in Cancer Treatment

Product	Indications
Nivolumab (Opdivo)	Lung/Kidney/Bladder/Hodgkins Lymphoma, Head/Neck, Melanoma, Colorectal, Liver
Pembrolizumab (Keytruda)	Lung/Melanoma/Cervical/Head/ Neck /Gastric/Hodgkins Lymphoma/Bladder/Liver
Durvalumab (Imfinzi)	Lung Cancer/ Urothelial Cancer
Ipiliumab (Yervoy)	Malignant Melanoma, Kidney Cancer
Atezolizumab (Tecentriq)	Lung Cancer, Breast Cancer, Urothelial Cancer
Avelumab (Bavencio)	Genitourinary Cancer, Urothelial Cancer
Cemiplimab (Libtayo)	Cutaneous Squamous Cell Carcinoma (CSCC)

PRODUCT	MODE OF ACTION
NIVOLUMAB	PD1 INHIBITION
PEMBROLIZUMAB	PD1 INHIBITION
ATEZOLIZUMAB	PD-L1 INHIBITION
AVELUMAB	PD-L1 INHIBITION
DURVALUMAB	PD-L1 INHIBITION
IPILIMUMAB	CTLA4 INHIBITION
CEMIPLIMAB	PD1 INHIBITION

IMMUNE CHECKPOINT INHIBITION

Adverse Events and Side Effects Management

- Can cause immune related adverse events due to overstimulation of immune reactivity (3 out of 10 patients) or generation of autoimmune phenomena.
- High fever/inflammatory reactions , skin, respiratory, gastrointestinal side effects, etc. Mild to life threatening.
- Patients should be made aware that they need to contact/hospital once a possible side effect occurs.

IMMUNE CHECKPOINT INHIBITION

- Resistance
  - Limits efficacy to treatment
    e.g. loss of PD-L1 ⟶ cause for resistance
- Overcoming Resistance
  - Combination with chemotherapy, radiotherapy,targeted therapies (e.g. tyrosine kinase inhibitors)
  - ↑ Efficacy, ↓ Resistance
- Limitation
  - Biomarkers
  - Access
  - Price

Immune Checkpoint Inhibition

- The Future?
- 1500 clinical trials in process.
- Expected to reach a 40 billion USD market by 2025.
- New hope for patients that used to have no alternative after chemo failed.
- Technology needs to be improved to identify biomarkers and patients most likely to benefit, reduce adverse events, improve access to more patients and find rational combinations.
- Other immune check points $\longrightarrow$ Future Targets

NEW DRUGS IN THE MANAGEMENT OF MIGRAINE

Migraine

- Affects around 15% of patients worldwide(more women than men, normally starts in late teens into the 50's)
- Majority of patients with acute migraines has episodic migraines (< 15 headache days/month and lasts 4-72 hours).

  2-3 attacks/month
- 3% of patients ⟶ chronic migraine > 15 headache days/month
- Typical symptoms: headache/ nausea/ vomitting/ photophobia, etc.(with or without aura)
- No specific diagnostic tests/diagnosis on patient history
- Pathophysiology not fully understood

Migraine

Available Treatment

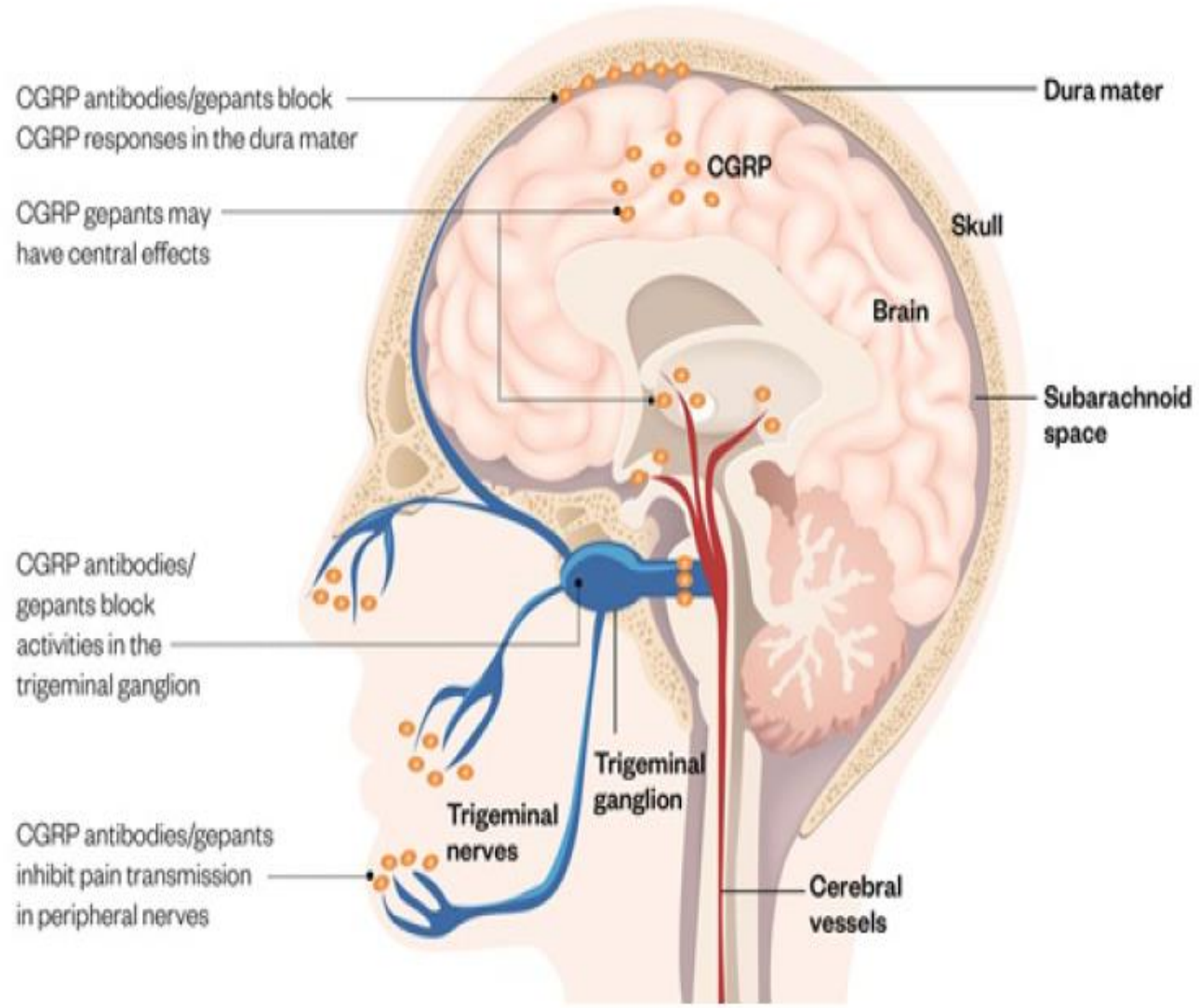
- Simple analgesia(paracetamol/ NSAIDs)
- Ergotamine based formulations
- 5HTI receptor agonists (triptans)
- Antiemetics can be used in patients with nausea and vomiting
- Prophylaxis for chronic migraine: propranolol, amitriptyline, etc.

Migraine – the CGRP story

- Several drugs that target calcitonin gene related peptide (CGRP), a small protein that acts as a neurotransmitter have shown promises in various clinical trial.
- Research has shown high levels (CGRP) in migraine attacks.
- CGRP blockers establish a new frontier in migraine management
- Vascular Theory v/s Neuronal Theory

Two types of CGRP blockers

- Monoclonal antibodies
- Small molecules (gepants)



TARGETING CGRP IN MIGRAINE.CGRP is present throughout the body and brain and spikes during migraine
Source: The Pharmaceutical Journal

ERENUMAB (AIMOVIG) is the first Monoclonal Antibody (CGRP blocker) approved for migraine

- USFDA/EMEA approval in 2018
- Blocks CGRP
- Injectable drug
- Effectiveness supported by 3 placebo controlled trials
- Novel option for reducing the number of days with migraine, a painful and often debilitating condition.

ERENUMAB

Mechanism of action:

- Binds to CGRP receptor and antagonizes CGRP receptor function.
- CGRP is involved in the pathophysiology of migraine through nociceptive mechanism in the trigeminovascular system.

ERENUMAB

Dosing and administration:

- 70mg once monthly (SC injection)
- May increase to 140mg (2 injections for some patients)

ERENUMAB

- Efficacy of Erenumab as a preventive treatment of episodic or chronic migraine was assessed in 3 randomized, double blind, placebo controlled studies.
  - 2 trials → episodic migraine (Strive, Arise)
  - 1 trial → chronic migraine

- Patients with a history of migraine, with or without aura

  Duration 3-6 months

  Average age: 42 years

Results (Efficacy)

- Patient with chronic migraine → average reduction of 2.5 monthly migraine days
- Patient with episodic migraine → average reduction of 3.2 to 3.7 days

ERENUMAB

Adverse events

- Most common (≥ 3% incidence) : injection site reactions, constipation
- No contraindications

Use in specific population

- No adequate data in pregnant women/lactation
- Safety not established in children
- Older patients (not studied)

ERENUMAB

- Offers patients a new option in reducing migraine days
- Hailed as a breakthrough therapy
- Safe profile

Limitation

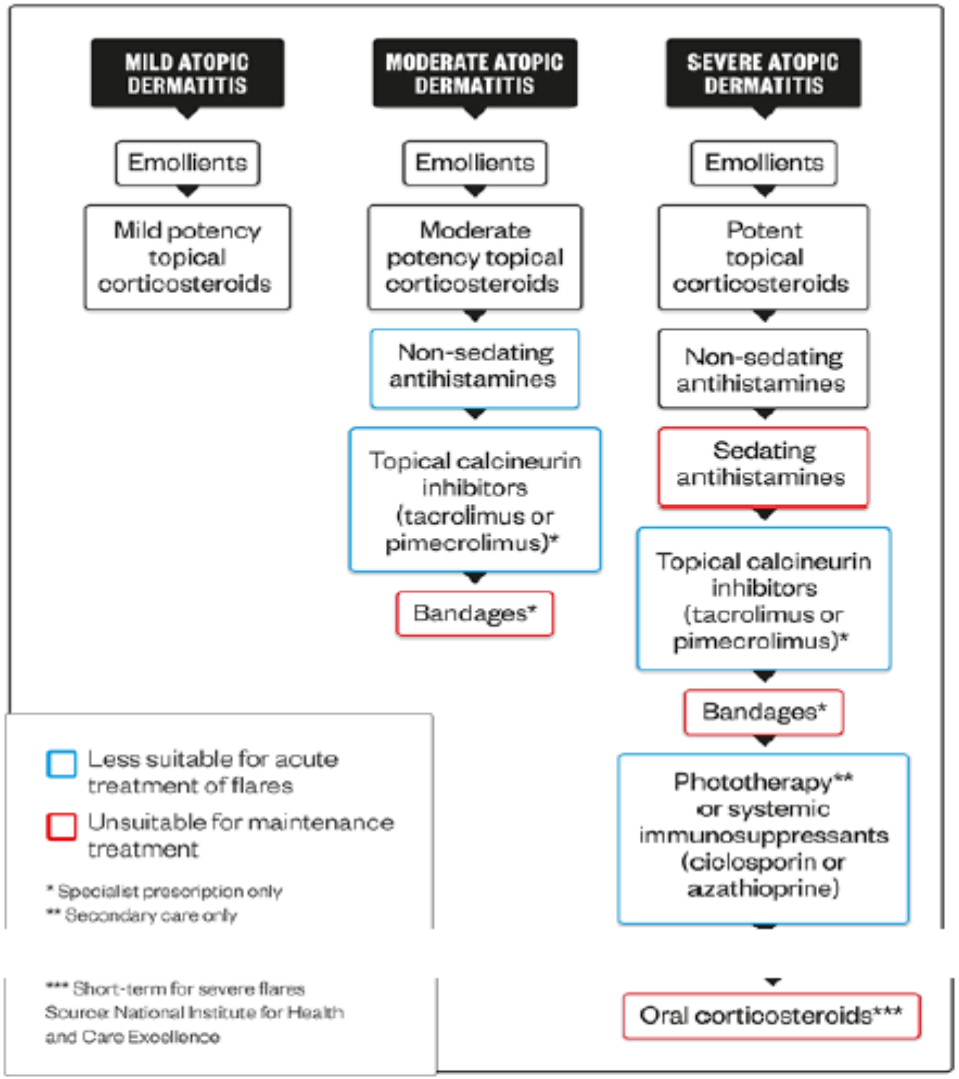
- Cost

Atopic Dermatitis

- A New Era

Atopic Dermatitis

- Affects 30% of children and 10% of adults
- 20% of patients suffer moderate to severe disease
- An important number of patients uncontrolled even with systemic drugs



Current stepped treatment options for atopic dermatitis

Treatment for atopic dermatitis can be stepped up or down depending on disease severity. Acute flares will often require a temporary increase in the intensity of treatment

Source: National Institute for Health and Care Excellence

Atopic Dematitis

- Despite the impact that atopic dermatitis has on patient's lives, there have been no major changes to the way the disease is treated in the past 15 years.

- Two new medicines herald a new era in its management

New drugs in the management of atopic dermatitis

- Dupilumab, a biologic for severe disease
- Crisaborole, a topical small molecule for milder disease.

The need for new treatment

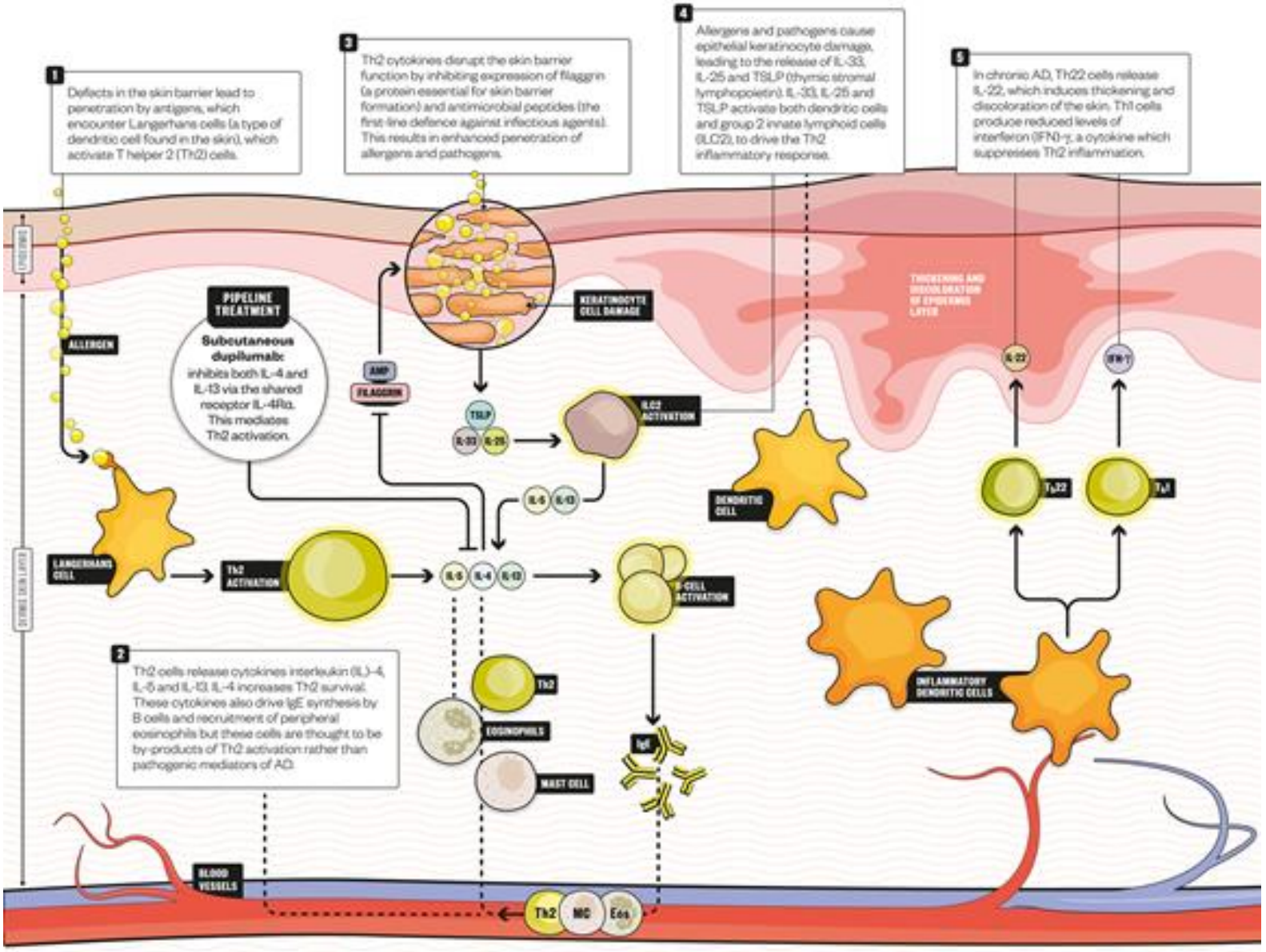
- Prevalence (30% children, 10% adults)
- ↑ Prevalence 3 fold since the 1950s
- An important proportion of patients is not controlled even with systematic treatment
- Quality of life poor, distressing disease
- Patients 3 times more likely to suffer depression

Atopic Dermatitis

- Two main pathological elements:
  - -impaired skin barrier function
  - -immune dysfunction
- Emollients target skin barrier dysfunction. Steroids, calcineurin inhibitors, systemic immunosuppression target the immune dysfunction
- Treatment applied to the skin → often used sub optimally (not enough application/ not as frequent)

DUPILUMAB (dupixent)

- A new drug for atopic dermatitis (eczema)
- Anticipated as a revolutionary treatment for patients wit severe eczema.
- Targets the Th2 pathway to inhibit the inflammatory response that drives atopic dermatitis
- Injection (SC Route)
- Mode of action – inhibition of interleukin (IL)4 – receptor alpha



HOW DUPULIMAB WORKS. TARGETS THE Th2 PATHWAY THAT DRIVES AD. Infographic: Alisdair McDonald Source: The Pharmaceutical Journal

DUPILUMAB

- Safety and efficacy established in 3 placebo controlled trial involving 2119 patients with moderate to severe atopic dermatitis not properly controlled by topical medication.

- After 16 weeks of treatment, the dupilumab arm of the trial achieved a great response and were defined as having clear or “almost clear” skin as well as reduction in itching.

DUPILUMAB

Common Side Effects

Injection Site Reactions

Cold Sores

Redness, Swelling and Itching around the eyes

Dosing and administration

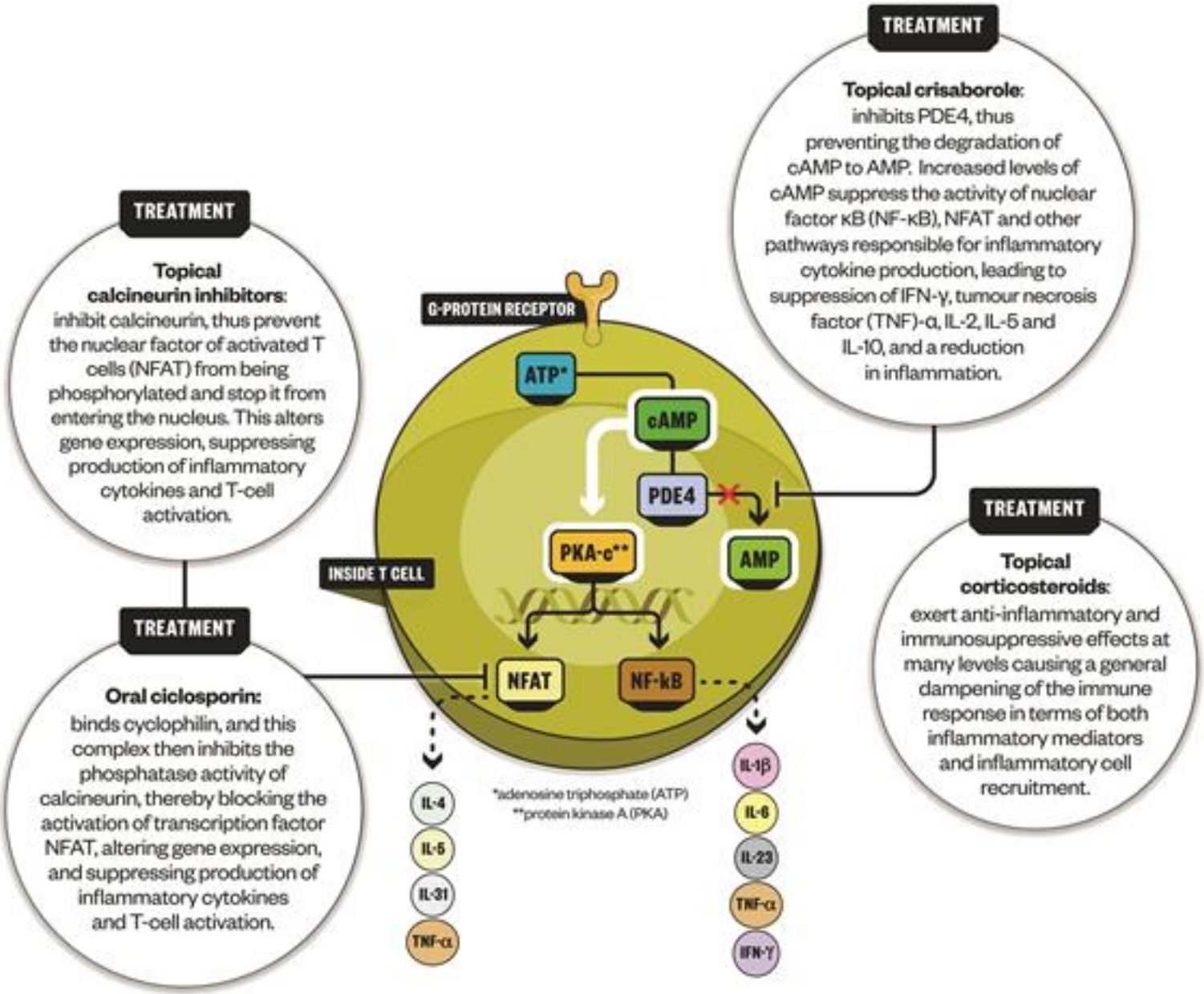
- Indicated for children above 12 years
- Subcutaneous injection every 2 weeks

DUPILUMAB

- USFDA/EMEA approval in 2018
- Heralded as a breakthrough therapy changing the lives of eczema patients
- Expansion of its indications: in asthma with eosinophilic phenotype/oral corticosteroid dependent asthma and chronic rhinosinusitis with nasal polyps.
- Studies ongoing in pediatric population, long term safety

CRISABOROLE (Eucrisa)

- In mild to moderate dermatitis in patients 2 years and older
- Topical treatment (non-steroidal ointment – twice daily application)
- Inhibition of phosphodiesterase 4 ⟶ role in atopic dermatitis
- Reduces the level of a number of cytokines involved in atopic dermatitis
- Suppresses the immune system activation



HOW CRISABOROLE WORKS.INHIBITION OF PHOSPHODIESTERASE 4(PDE4), ROLE IN AD.
Infographic: Alisdair Mc Donald Source:The Pharmaceutical Journal

CRISABOROLE

- No serious adverse events
- Main side effect: burning/stinging at site of application.
- Effectiveness shown in phase III trials conducted in the US
- Approved by FDA in 2017
- Should fill the niche that steroids and calcineurin inhibitors currently leave open resulting from fears over side effects.

Miscellaneous breakthroughs

1. Brexanolone(Zulresso) :
   - post partum depression
   - Continuous infusion over 60 hours(2.5 days)
   - Monitored in a healthcare setting for sedation/hypoxia

2. Onasemnogene abeparvovec - (Zolgensma)

First gene therapy to treat children less than 2 years old with spinal muscular atrophy (SMA), the most severe form of SMA/ leading cause of infant mortality. IV inf/ 60 mins. Single dose

3. Valbenazine (Ingrezza)
- Tardive Dyskinesia
- 32% with typical antipsychotics and 13% with atypical antipsychotics patients suffer this iatrogenic side effect
-Oral treatment

4. Transtuzumab Emtansine(Kadclya)

- HER 2 positive breast cancer
- antibody – drug conjugate
- IV infusion therapy

5. Lumacaftor/Ivacaftor (Orkambi)
- Cystic fibrosis
- Oral Treatment

6. Fingolimod (Glienya)
- Multiple Sclerosis
- Oral Treatment

Thank you