RECENT ADVANCES IN THERAPEUTICS

- ATOPIC DERMATITIS
- MIGRAINE
- IMMUNOTHERAPY FOR CANCER
- ATMP DRUGS
- URINARY INCONTINENCE
- MISCELLANEOUS BREAKTHROUGHS

MEDICAL UPDATE GROUP
SADECK VAWDA

October 2022

1. ATOPIC DERMATITIS

- 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.

- Three new medicines herald a new era in its management

NEW DRUGS IN THE MANAGEMENT OF ATOPIC DERMATITIS

- Dupilumab, a biologic for moderate to severe disease (Dupixent).
- Crisaborole, a topical small molecule for milder disease (Eucrisa).
- Baricitinib, a Janus kinase inhibitor

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 systemic treatment
- Quality of life poor, distressing disease
- Patients 3 times more likely to suffer depression

ATOPIC DERMATITIS

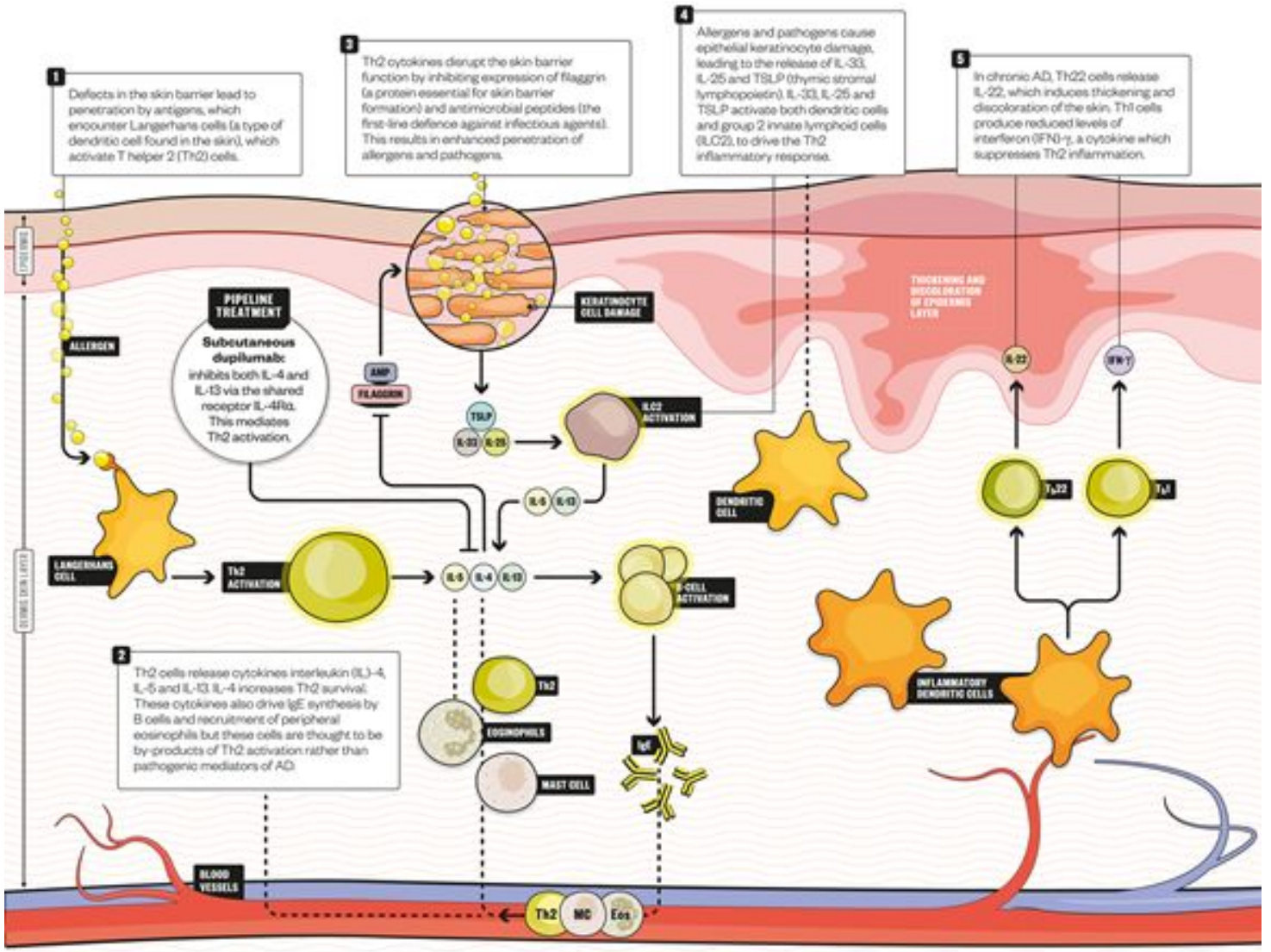
Two main pathological elements: Impaired skin barrier function and immune dysfunction

- Emollients target skin barrier function
- 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

- A new drug for atopic dermatitis (eczema)
- Anticipated as a revolutionary treatment for patients with severe eczema.
- Targets the Th2 pathway to inhibit the inflammatory response(release of cytokines-interleukins)that drives atopic dermatitis
- Injection (SC Route)
- Mode of action – inhibition of interleukin (IL)4 – receptor alpha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Defects in the skin barrier lead to penetration by antigens, which encounter Langerhans cells (a type of dendritic cell found in the skin), which activate T helper 2 (Th2) cells.
3
Th2 cytokines disrupt the skin barrier function by inhibiting expression of filaggrin (a protein essential for skin barrier formation) and antimicrobial peptides (the first-line defence against infectious agents). This results in enhanced penetration of allergens and pathogens.
4
Allergens and pathogens cause epithelial keratinocyte damage, leading to the release of IL-33, IL-25 and TSLP (thymic stromal lymphopoietin). IL-33, IL-25 and TSLP activate both dendritic cells and group 2 innate lymphoid cells (ILC2), to drive the Th2 inflammatory response.
5
In chronic AD, Th22 cells release IL-22, which induces thickening and discoloration of the skin. Th1 cells produce reduced levels of interferon (IFN)-γ, a cytokine which suppresses Th2 inflammation.
PIPELINE TREATMENT
Subcutaneous dupilumab: inhibits both IL-4 and IL-13 via the shared receptor IL-4Rα. This mediates Th2 activation.
ALLERGEN
AMP
FILAGGRIN
KERATINOCYTE CELL DAMAGE
TSLP
IL-33
IL-25
ILC2 ACTIVATION
IL-5
IL-13
DENDRITIC CELL
THICKENING AND DISCOLORATION OF EPIDERMIS LAYER
IL-22
IFN-γ
Th22
Th1
LANGERHANS CELL
Th2 ACTIVATION
IL-5
IL-4
IL-13
B-CELL ACTIVATION
INFLAMMATORY DENDRITIC CELLS
2
Th2 cells release cytokines interleukin (IL)-4, IL-5 and IL-13. IL-4 increases Th2 survival. These cytokines also drive IgE synthesis by B cells and recruitment of peripheral eosinophils but these cells are thought to be by-products of Th2 activation rather than pathogenic mediators of AD.
Th2
EOSINOPHILS
MAST CELL
IgE
BLOOD VESSELS
Th2
MC
Eos

DUPILUMAB

- Safety and efficacy established in 3 placebo-controlled trials 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 was 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 6 years
- Subcutaneous injection every 2 weeks

DUPILUMAB

- USFDA/EMEA approval
- Heralded as a breakthrough therapy changing the lives of eczema patient
- Expansion of its indications: in asthma with eosinophilic phenotype/oral corticosteroid dependent asthma, chronic rhinosinusitis with nasal polyps, and esonophilic esophagitis.
- Approved in children aged 6 years and older, studies ongoing 6 months-5 years
- A 2nd biological drug (tralokinumab – also approved (interleukin 13 inhibitor)

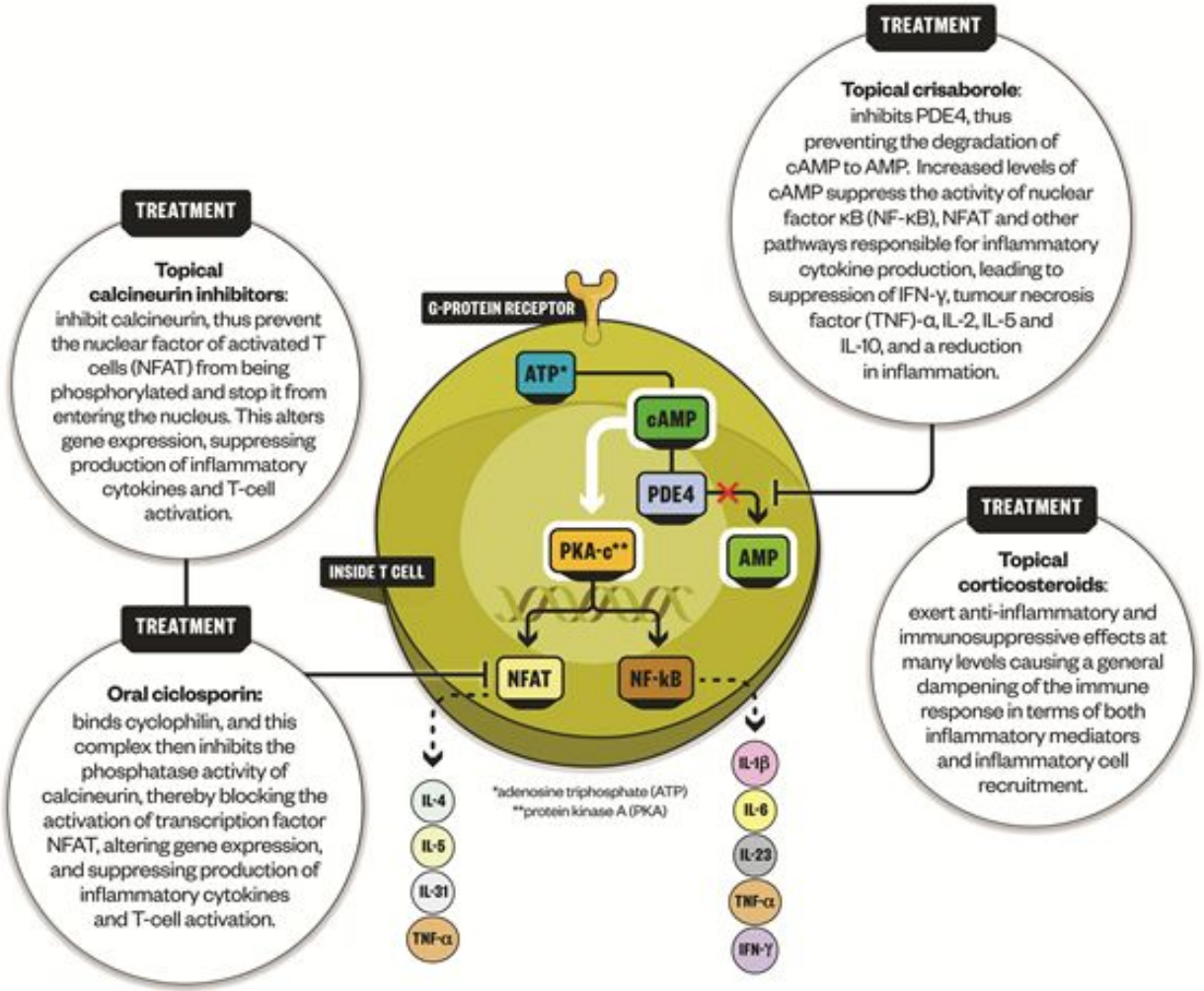
DUPILUMAB

- Indicated in patients aged 6 years and above with moderate to severe atopic dermatitis not adequately controlled by topical preparations or when these therapies are not advisable

- Can be used with or without topical steroids

CRISABOROLE

- In mild to moderate dermatitis in patients 3 months 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


TREATMENT
Topical crisaborole:
inhibits PDE4, thus preventing the degradation of cAMP to AMP. Increased levels of cAMP suppress the activity of nuclear factor κB (NF-κB), NFAT and other pathways responsible for inflammatory cytokine production, leading to suppression of IFN-γ, tumour necrosis factor (TNF)-α, IL-2, IL-5 and IL-10, and a reduction in inflammation.
TREATMENT
Topical calcineurin inhibitors:
inhibit calcineurin, thus prevent the nuclear factor of activated T cells (NFAT) from being phosphorylated and stop it from entering the nucleus. This alters gene expression, suppressing production of inflammatory cytokines and T-cell activation.
G-PROTEIN RECEPTOR
ATP*
cAMP
PDE4
PKA-c**
AMP
INSIDE T CELL
NFAT
NF-kB
TREATMENT
Topical corticosteroids:
exert anti-inflammatory and immunosuppressive effects at many levels causing a general dampening of the immune response in terms of both inflammatory mediators and inflammatory cell recruitment.
TREATMENT
Oral ciclosporin:
binds cyclophilin, and this complex then inhibits the phosphatase activity of calcineurin, thereby blocking the activation of transcription factor NFAT, altering gene expression, and suppressing production of inflammatory cytokines and T-cell activation.
IL-4
IL-5
IL-31
TNF-α
IL-1β
IL-6
IL-23
TNF-α
IFN-γ
*adenosine triphosphate (ATP)
**protein kinase A (PKA)

CRISABOROLE

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

JANUS KINASE (JAK) INHIBITORS IN ATOPIC DERMATITIS

- Baricinitib (OLUMIANT)
- Adrocitinib (CIBINQO)
- Upadacitinib (RINVOQ)

- Small molecules, Oral therapy.

JANUS KINASE (JAK) INHIBITORS IN ATOPIC DERMATITIS

- The JAK family of Tyrosine Kinases include 4 members (JAK1, JAK2, JAK3,TYK2), depending on their selectivity for one or several JAKs
- Janus Kinases (JAKs) are enzymes that transduce intra cellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function.
- Exert a broad immunopharmacological impact.
- 3 products approved in AD
  - Dual inhibitors (baricitinib) – JAK1/JAK2 inhibitor
  - JAK1 inhibitor (abrocitinib, upadacitinib)

BARICITINIB (OLUMIANT)

- Approved by EMA
- Indications: AD, Rheumatoid Arthritis, Alopecia Areata
- Oral therapy
- Approved as EUA for treating severe COVID-19 patients who require breathing help.
- Also indicated in some other autoimmune disorders: RA, alopecia aerata

BARICITINIB

- Indicated for treatment of moderate to severe Atopic Dermatitis in adult patients who are candidates for system therapy.
- Recommended dose is 4mg once daily.
- Consideration should be given to discontinuing treatment for patients who show no evidence of therapeutic benefit after 8 weeks.
- Efficacy can be enhanced when given with topical corticosteroids.

BARICITINIB

- Serious infections have occurred in patients receiving baricitinib
- Avoid use in patients with know active tuberculosis
- Avoid use of live vaccines
- We need to consider the risks and benefits prior to initiating therapy in patients with chronic or recurrent infection / acute infection
- Closely monitor patients for infections during therapy: UTI, herpes zoster, pneumonia, etc.
- Thrombosis
- Blood screening prior to initiation (neutropenia, etc).

- Two other Janus Kinase inhibitors now recommended by NICE for moderate to severe atopic dermatitis in adults and young people > 12 years

- Abrocitinib and upadacitinib

2. MIGRAINE

MIGRAINE

- Affects around 15% of patients worldwide
- Majority of patients with acute migraines has episodic migraines (< 15 headache/month and lasts 4-72 hours).

  2-3 attacks/month
- 3% of patients → chronic migraine > 15 headache days/month
- Typical symptoms: headache/ Nausea/ Vomiting/ Photophobia, etc.
- No specific diagnostic tests/diagnosis on patient history
- Prodrome stage(yawning, irritability, mood changes, etc), then headache with or without aura(neurological symptoms-visual, motor)

PATHOPHYSIOLOGY

- Unknown
- Characterised by dysfunction of sensory processing
- Vasodilation?
- Neurogenic inflammation?
- Gene mutations/genetic component

MIGRAINE MANAGEMENT

- Acute treatment: control symptoms and improve quality of life
  Start with simple analgesia, escalate to 5HT1 agonist if treatment failure.
  Anti-emetics in patients with nausea/vomiting associated with migraine.

- Prophylaxis for patients with chronic migraine.
  Choice of drug based on patient's co-morbidities and side effects profile.
  Reduce number, severity and duration of migraine attacks

MIGRAINE

Trigger Factors

- Diet(Spicy food ,alcohol, cheese)
- Change in habit (missing meals, sleep, long distance travel, etc)
- Stress
- Hormonal changes (menstruation)
- Strenuous exercise or routine physical activity.

Lifestyle changes should be encouraged in order to avoid triggers where possible.

Behavioural(relaxation), physical therapy : (physio, neuromodulation, etc) useful.

MIGRAINE

Available Treatment

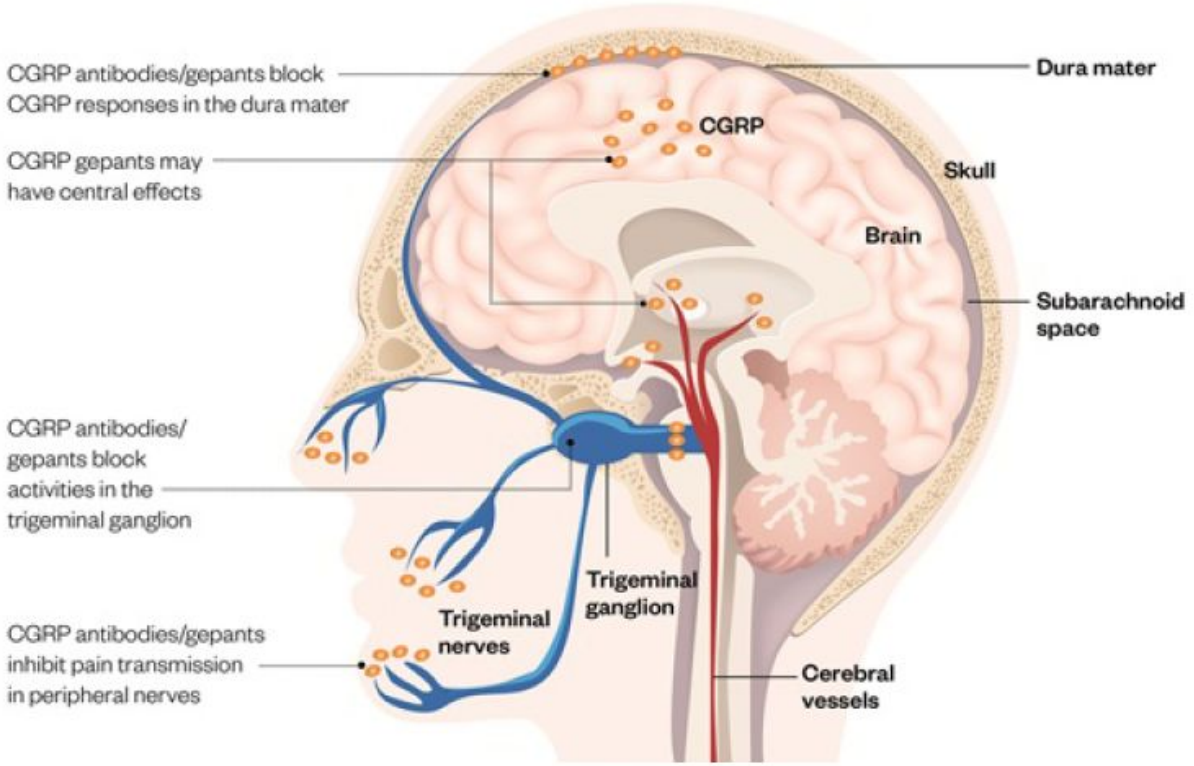
- Simple analgesia(paracetamol/NSAIDS)
- Ergotamine based formulations- cerebral vasoconstriction
- 5HTI B and D receptor agonists (triptans)- SC, oral, nasal-Significant pain relief -30% of non responders. Not to be used in cardiovascular patients
- Anti-emetics can be used in patients with nausea and vomiting
- Prophylaxis for chronic migraine: propranolol, amitriptyline, topiramate, sodium valproate, botulinum toxin, etc.
- Pregnancy (paracetamol)
- Codeine not to be used (gastric stasis)

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 trials.
- Research has shown high levels (CGRP) during 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)


CGRP antibodies/gepants block CGRP responses in the dura mater
CGRP gepants may have central effects
CGRP antibodies/ gepants block activities in the trigeminal ganglion
CGRP antibodies/gepants inhibit pain transmission in peripheral nerves
Dura mater
CGRP
Skull
Brain
Subarachnoid space
Trigeminal ganglion
Trigeminal nerves
Cerebral vessels

ERENUMAB (AIMOVIG)

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

- USFDA/EMEA approval
- 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)
- Preventive treatment in patients with at least 4 migraine days/month

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
- Elderly (not studied)

ERENUMAB

- Offers patients a new option in reducing migraine days
- Safe profile

Limitation

- Cost- 600 USD /dose

OTHER CGRP BLOCKERS

Three other CGRP blockers approved recently(monoclonal antibodies):

- Fremanezumab (Ajovy)
- Galcanezumab (Emgality)
- Epitinezumab (Vyepti)

SMALL MOLECULES-GEPANTS

RIMEGEPANT (NURTEC)

- A new oral drug for management of migraine.
- Calcitonin gene related peptide antagonist for management of acute migraine.

RIMEGEPANT

- US FDA approval
- Orally disintegrating tablet for sublingual/oral use
- Single oral dose
- Fast acting (within one hour)
- Sustained efficacy (lasts up to 24 hours)
- Adverse effects: Nausea, UTI.
- Also indicated in migraine prevention- on alternate days

Ubrogepant (Ubrelvy) and Atogepant (Qulipta) recently approved

LASMIDITAN (A DITAN) (REYVOW)

- New class of oral drugs (ditans) to treat acute migraine
- First of this class to hit the market in February 2021
- 5HT1-F agonist, one dose per 24 hours
- May be recommended when a triptan fails or due to risks of co-morbidities (no vasoconstrictions so safer with people with heart problems)
- Common side effects: dizziness, tiredness, numbness (advise not to drive/operate machinery within 8 hours of dose)
- Controlled drug (addiction issues)

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(HER2), 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 staged with much higher efficiency and durability).

4 TYPES OF IMMUNO-ONCOLOGY THERAPY

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

1. 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 treatments were ineffective.

CAR T CELL THERAPY

Two Car T Therapies were approved by USFDA since 2019

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

Recently approved (Tecartus, Breyanzi, Abecma, Carvykti)

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 2019.
- 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

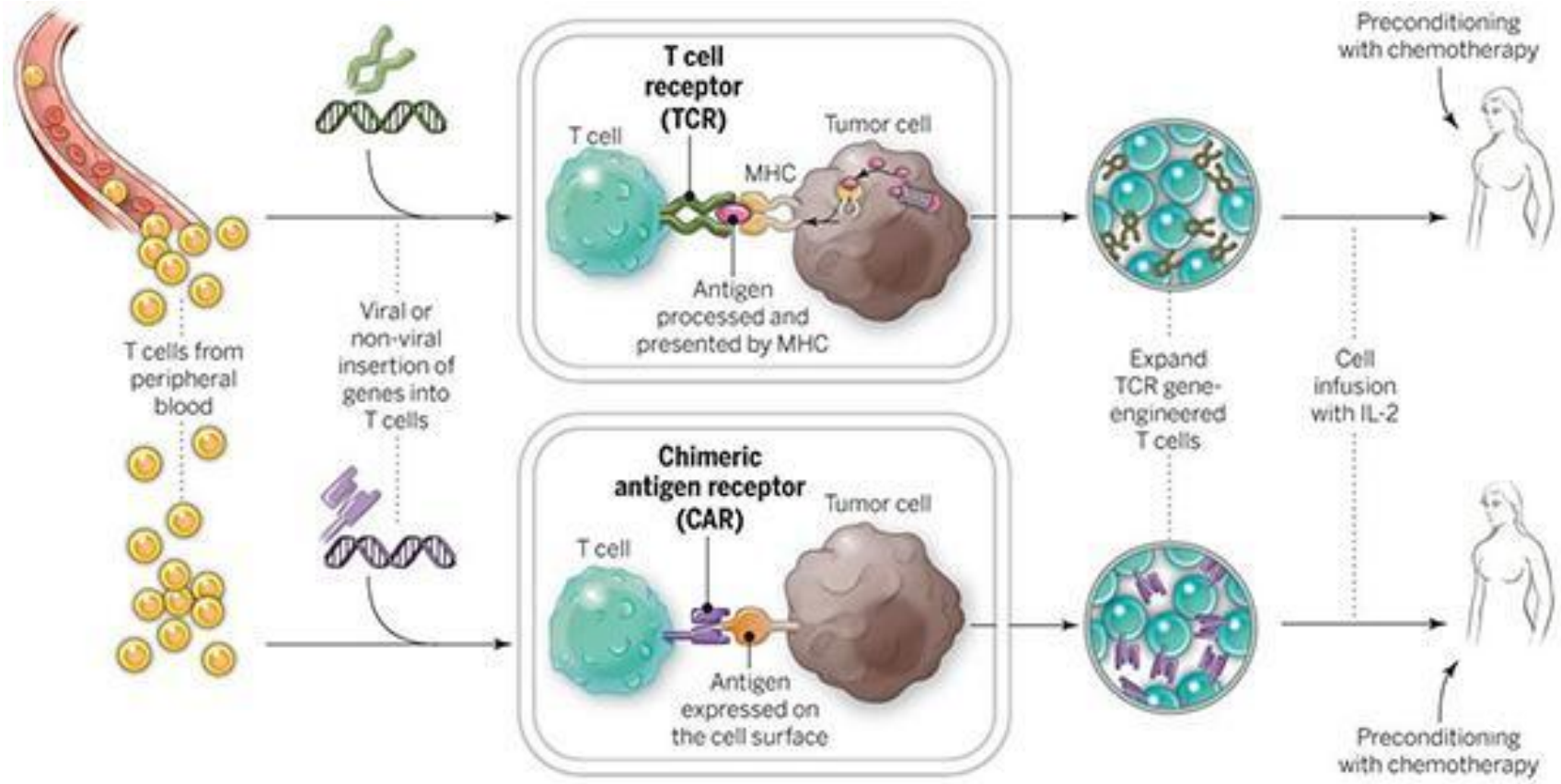
- Like all cancer therapies, CAR T-Cell therapy can cause several worrisome and sometimes fatal side effects.
- One of the most frequent is Cytokine Release Syndrome (CRS).
- Cytokines are released by T Cells as part of their immune duties to stimulate and direct the immune system.
- In CRS, there is 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 1L-6, a cytokine secreted by T-Cells.
- Tocilizumab (Actemra) which blocks 1L-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.

CarT cells are engineered to produce special receptors on their surfaces. They are then expanded in the lab and returned to the patient.



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 have 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.

ADCS(ANTIBODY DRUG CONJUGATES)

- Chemotherapy has a significant clinical benefit for many tumours, but it has low selectivity with potential toxic side effects
- Antibody drug conjugates(ADCs)are a promising cancer treatment that includes delivering cytotoxic drugs to specific tumour cells that exhibit specific antigens .
- The antibody, cytotoxic agent and linker are the three primary structural units of an ADC
- ADCs are expected to provide powerful therapeutic modalities against various cancers by combining the selectivity of monoclonal antibodies(mAbs) and the efficacy of various chemotherapeutics
- To date 14 ADCs have received market approval and more than 100 are in pre-clinical and clinical trials

ADCS(SOME EXAMPLES)

- Adcetris(Brentuximab vedotin)- Classical Hodgkin Lymphoma, certain T-cell lymphomas
- Kadclya(ado-transtuzumab emtansine)-HER2 positive metastatic breast cancer/early breast cancer
- Enhertu(fam-transtuzumab deruxtecan –nxki)-HER2+ metastatic breast cancer ,HER2 low metastatic breast cancer, HER2+ metastatic stomach cancer and HER2mutant metastatic lung cancer)

IMMUNE CHECK POINTS

- 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-L1)

- 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 CHECK POINT INHIBITORS USED IN CANCER TREATMENT

Product	Indications
Nivolumab (Opdivo)	Lung/Kidney/Bladder/Hodgkins Lymphoma, Head/Neck Cancer, Melanoma, Colo Rectal/Liver
Pembrolizumab (Keytruda)	Lung Cancer/Melano/Cervical/Head/ Neck Cancer/Castric/Hodgkins Lymphoma/Bladder/Liver
Durvalumab (Infinzi)	Lung Cancer/ Urothelial Cancer
Ipiliummab (Yervoy)	Malignant Melanoma, Kidney Cancer
Atezolizumab (Tecentriq)	Lung Cancer, Breast Cancer, Urothelial Cancer
Avelumab (Bravencio)	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	QD1 INHIBITION

IMMUNE CHECK POINT 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 auto immune phenomena.
- High fever/inflammatory reaction , skin, respiratory, gastrointestinal, etc. mild to life threatening.
- Patients should be made aware that they need to contact/hospital once a possible side effect occurs.

IMMUNE CHECK POINT 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 CHECK POINT 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 → Future Targets

CANCER VACCINES

- Preventive: HPV vaccine, HepB vaccine
- Therapeutic : BCG vaccine- bladder cancer , Povenge(sipuleucel-T) for certain men with advanced prostate cancer).
- Many clinical trials ongoing for a range of therapeutic vaccines in various tumours

4. ATMP Drugs (Advanced therapy medicinal drugs)

- New class of medicinal drugs
- 3 Principal Categories
  - Medicines for gene therapy
  - Products based on somatic cell therapy
  - Tissue engineered products

Medicines referred to as “combined ATMPs” may incorporate a medical device.

ATMPS

ATMPs

- challenges and opportunities

Challenges - preparation, storage and prescription

- licensing, processes, assessing cost-effectiveness

Opportunities - hope, opportunity and clinical optimism to diagnoses (diseases that have unmet needs/devastating prognoses).

ATMPS

- Gene Therapy
  - Incorporate genes that can bring about an effect that is diagnostic, prophylactic or therapeutic.
  - Insert in the body so called “recombinant genes (stretches of DNA from different sources and produced in a laboratory setting)
  - Objective of treating genetic disorders, cancer and chronic diseases.
  - Virus based gene therapies and cell based gene therapies.

(Virus as a vector)

(Donor cells undergoing genetic modifications)

ATMPS

- Products based on somatic cell therapy. These comprise either substantially manipulated cells or tissues in which their biological characteristics have been altered to produce actions different from their normal function.

- Tissue engineered cells
  - Based on modified cells/tissues with the objective of repairing, replacing and regenerating human tissue.

Name of ATMP	Type of ATMP	Indication	Product manufacture and administration	Efficacy (major outcome trials)
Atidarsagene autotemcel (Libmeldy)	Gene therapy medicinal product	Metachromatic leukodystrophy with mutations in the arylsulfatase A (ARSA) gene	• Autologous gene therapy manufactured with patient's own CD34+ stem cells, collected by leukapheresis or bone-marrow harvest, which are modified ex vivo using a lentiviral vector to insert a functional ARSA gene; • Single-dose administration.	Results indicate it is effective in modifying the disease course of early-onset metachromatic leukodystrophy in most patients
Autologous anti-CD19-transduced CD3+ cells (Tecartus)	Gene therapy medicinal product	Relapsed or refractory mantle cell lymphoma	• Autologous CAR-T cell therapy manufactured using the patient's own T-lymphocytes collected by leukapheresis; • The T cells are genetically modified ex vivo using a retroviral vector to produce anti-CD19 CAR-T cells; • The CAR-T cells are expanded and infused back into patient; • Single-dose administration.	In the phase 2 ZUMA-2 trial, after a minimum of 7 months of follow up, 93% of patients had an objective response, with 67% achieving complete response
Axicabtagene ciloleucel (Yescarta)	Gene therapy medicinal product	Relapsed/refractory diffuse large B-cell lymphoma and primary (DLBCL) mediastinal large B-cell lymphoma following two or more previous systemic treatments	• Product manufacture is similar to that described for Tecartus; • Single-dose administration.	In the phase 2 ZUMA-1 trial, after a median follow up of 24 months, 74% of patients achieved an objective response and 54% a complete response
Tisagenlecleucel (KYMRIAH)	Gene therapy medicinal product	Relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r ALL) in patients aged under 25 years Refractory DLBCL after more than 2 previous therapies	• Autologous CAR-T cell therapy manufactured using the patient's own T-lymphocytes collected by leukapheresis. The T cells are genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 CAR protein; • Single-dose administration.	• In the ELIANA trial, children and young adults with r/r ALL had an overall remission rate of 82.3%; • In the JULIET trial, adult patients with DLBCL demonstrated an overall response rate 53% at a median follow-up of 40.3 months
Talimogene laherparepvec (Imlygic)	Gene therapy medicinal product	Adult patients with unresectable metastatic melanoma	• Produced by recombinant DNA technology in Vero cells; • The exact mechanism of action is unknown, although when talimogene is injected into melanoma, it causes tumor lysis and release of tumor-derived antigens. This together with virally derived granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes an anti-tumor immune response.	In the OPTiM study, talimogene laherparepvec monotherapy versus GM-CSF showed a statistically significant durable response rate (19% vs. 1.4%) and overall response rate (31.5% vs. 6.4%). Median overall survival was 23.3 versus 18.9 months. 50 patients (16.9%) vs 1 patient (0.7%) achieved complete response in each group
Autologous human corneal epithelial cells (Holoclar)	Tissue-engineered medicinal product	Adult patients with moderate to severe limbal stem cell deficiency	• Autologous limbal stem cells. Collected at biopsy, expanded and implanted into the cornea; • Process takes several weeks.	The HLSTM01 trial reported 72.1% of patients had successful Holoclar transplant at 12 months after therapy
Voretigene neparvovec (Luxturna)	Gene therapy medicinal product	Inherited retinal dystrophies caused by RPE65 gene mutations	Extracted from naturally occurring adeno-associated virus and recombinant DNA techniques	The phase 3 301 study reported improvement in the visual acuity of at least 0.3 logMAR in 55% of first-treated eyes and 20% of second-treated eyes after 12 months
Autologous CD34+ enriched cell fraction containing CD34+ cells transduced with retroviral vector encoding for human adenosine deaminase cDNA sequence (Strimvelis)	Gene therapy medicinal product	Adenosine deaminase deficiency (severe combined immunodeficiency)	• Autologous bone-marrow-derived cells (CD34+ cells) collected and modified to make functional adenosine deaminase enzyme; • Single-dose administration.	The ADA15G01 trial reported a 100% survival rate at 3 years
Autologous chondrocyte implantation (ACI) using chondrosphere (Spherox)	Tissue-engineered medicinal product	Symptomatic articular cartilage defects of the knee	• Patient's own chondrocytes isolated from healthy cartilage then cultured in vitro for autologous use; • Entire process takes six to eight weeks.	A phase 3 licensing study demonstrated the non-inferiority of ACI (compared with microfracture) at 60 months follow-up
Onasemnogene abeparvovec (Zolgensma)	Gene therapy medicinal product	Spinal muscular atrophy	• Derived from human embryonic kidney cells by r-DNA technology; • Single-dose administration.	In the AVXS-101-CL-303 study, 21/22 patients survived event-free (without permanent ventilation) to >10.5 months of age and 20 survived to 18 months of age

Table 1: Type, mechanism of action, indication, manufacture and efficacy of ATMPs licensed in the UK

ATMPS

SOURCE: PHARMACEUTICAL JOURNAL 12 AUG 2022

ATMPS

- Future of medicine
- ATMPs have already delivered exciting outcomes and promise to deliver more in the future
- Life changing opportunities for many patients
- Challenges and opportunities (clinical, regulatory, health economics, quality)
- Prohibitive cost

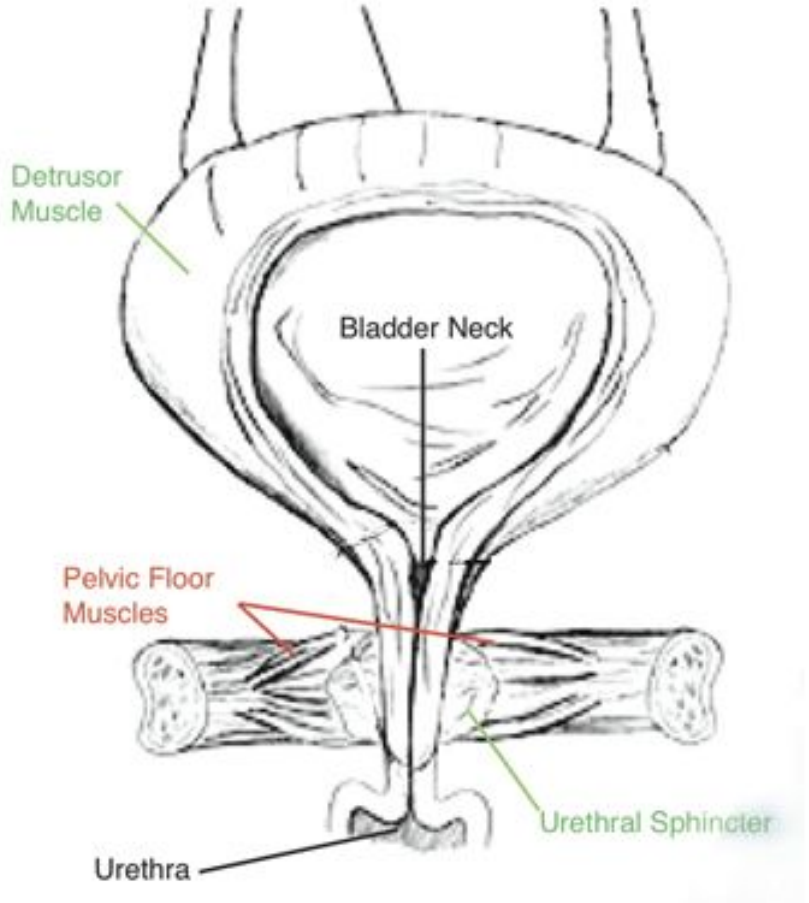
MANAGEMENT OF URINARY INCONTINENCE

5 . URINARY INCONTINENCE

TYPES OF URINARY INCONTINENCE

- STRESS INCONTINENCE
- URGE INCONTINENCE
- OVERFLOW INCONTINENCE
- MIXED INCONTINENCE (A COMBINATION OF URGE/STRESS INCONTINENCE)
- OTHER FORMS (E.G NOCTURNAL ENURESIS)

THE BLADDER MECHANISM



STRESS INCONTINENCE

- CAUSED BY AN INCOMPETENT URETHRAL SPHINCTER THAT ALLOWS LEAKAGE OF URINE WHEN PRESSURE IS RAISED IN BLADDER SUDDENLY (E.G EXERCISING, LIFTING, COUGHING, ETC)
- CAUSES OF URETHRAL SPHINCTER INCOMPETENCE INCLUDE DIRECT DAMAGE TO THE PELVIC FLOOR MUSCLES (OFTEN ASSOCIATED WITH CHILDBIRTH), POST MENOPAUSAL OESTROGEN DEFICIENCY AND IN MEN PROSTATECTOMY OPERATIONS
- AGGRAVATED BY WEAK PELVIC FLOOR MUSCLES, OBESITY, CHRONIC COUGHS, ALPHA BLOCKING DRUGS (WHICH RELAX THE URETHRAL SPHINCTER), PREMENSTRUAL HORMONE FLUCTUATIONS AND EXERCISE

URGE INCONTINENCE

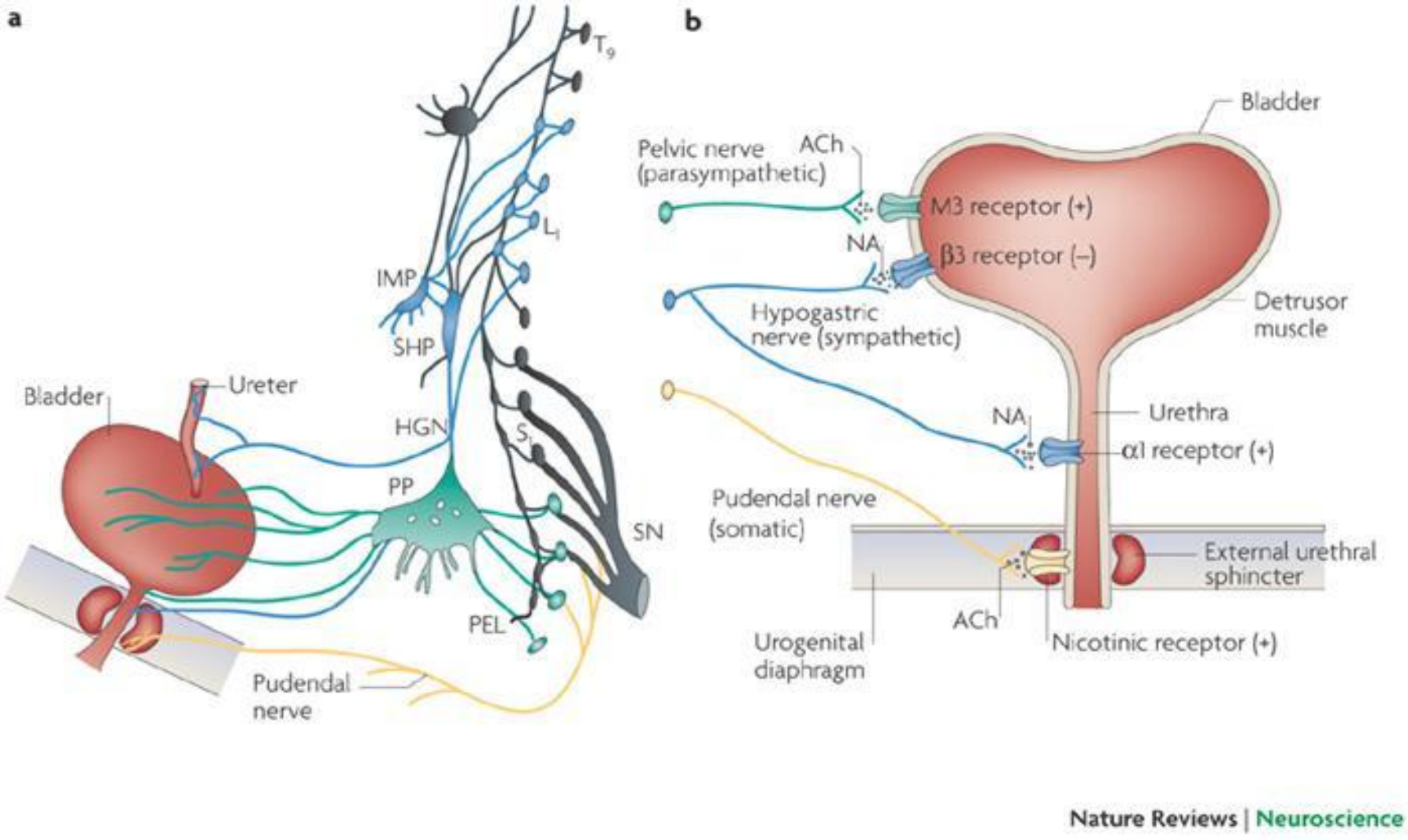
- CAUSED BY OVERACTIVITY OF THE DETRUSOR MUSCLE (BLADDER WALL)
- MANIFESTED AS URINARY URGENCY AND/OR FREQUENCY WITH OR WITHOUT INCONTINENCE, AND AS NOCTURIA
- DETRUSOR HYPERACTIVITY MAY BE IDIOPATHIC BUT IT MAY HAVE A NEUROPATHIC ORIGIN SUCH AS BRAIN INJURY OR CEREBROVASCULAR ACCIDENT
- CAN BE AGGRAVATED BY ANXIETY, ALCOHOL, ETC

OVERFLOW INCONTINENCE

- PATIENT WILL PROBABLY HAVE NOCTURIA AND REPORT PASSIVE DRIBBLING OF URINE, FREQUENCY, INCOMPLETE BLADDER EMPTYING
- A COMMON CAUSE IS OUTFLOW OBSTRUCTION DUE TO BENIGN PROSTATIC HYPERTROPHY (BPH) OR CANCER OF THE PROSTATE

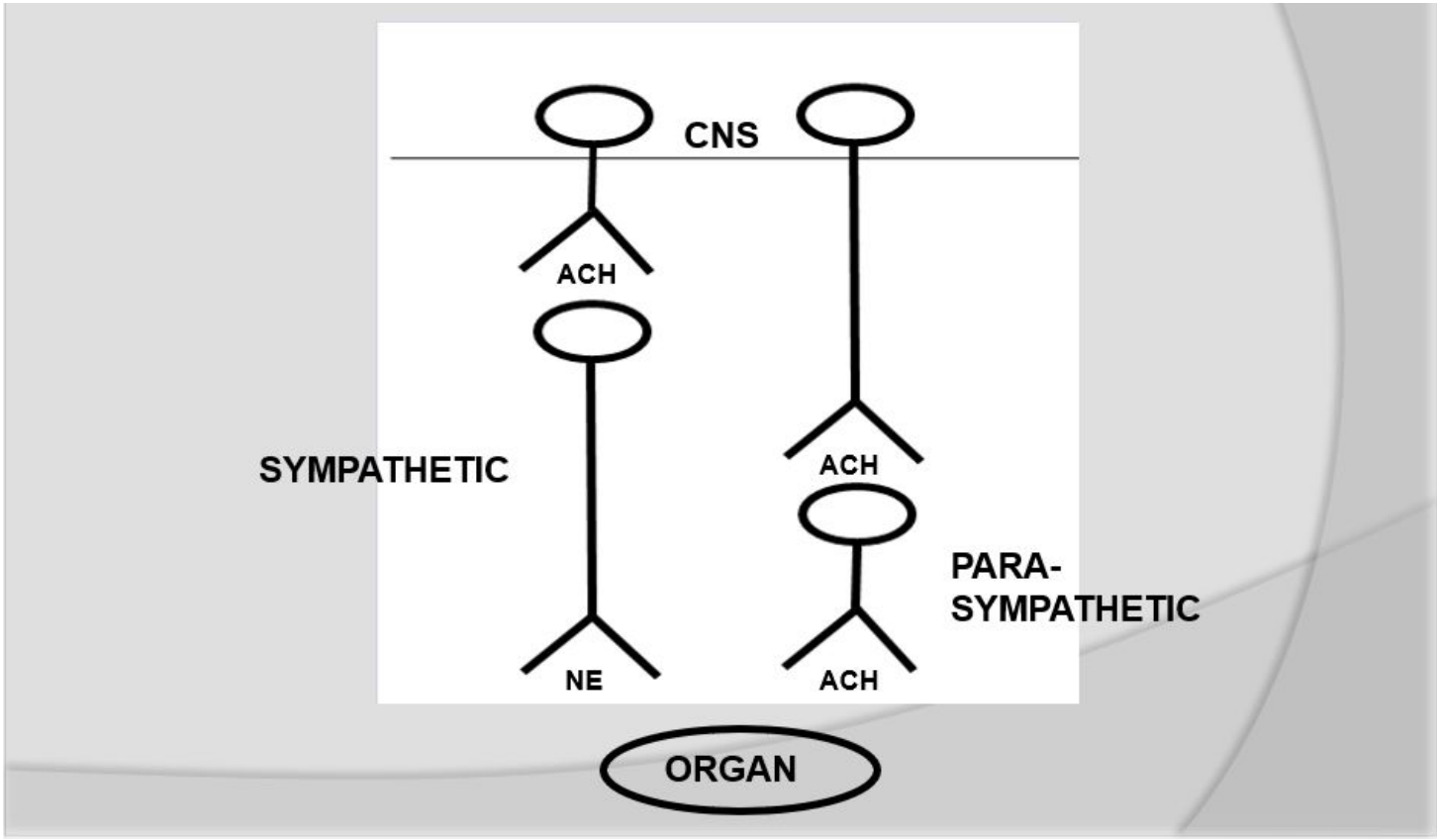
PHARMACOLOGICAL CAUSES

- ANY INCONTINENT PATIENT SHOULD HAVE THEIR MEDICATION REVIEWED TO CHECK WHETHER SIDE EFFECTS OF DRUGS ARE A CONTRIBUTING FACTOR TO THEIR PROBLEM
- THESE INCLUDE FOR EXAMPLE ALPHA BLOCKERS, DIURETICS
- CAFFEINE MAY AGGRAVATE DETRUSOR OVERACTIVITY AND ALCOHOL CAN CAUSE DIURESIS, BOTH LEADING TO URGE INCONTINENCE



Nature Reviews | Neuroscience

DUAL INNERVATION OF URINARY BLADDER



MANAGEMENT OF URGE INCONTINENCE

- DECREASING CAFFEINE AND ALCOHOL INTAKE
- PELVIC FLOOR EXERCISES
- BLADDER RETAINING (PATIENTS ENCOURAGED TO KEEP A BLADDER RECORD CHART WHICH RECORDS WHEN URINE IS PASSED NORMALLY AND ANY LEAKAGE) – AIM IS TO INCREASE TIME BETWEEN VISITS OR VOLUME PASSED EACH TIME
- DRUG THERAPY: MOST EFFECTIVE DRUGS ARE ANTICHOLINERGICS WHICH RELAXES DETRUSOR MUSCLES
- OPTIONS INCLUDE: OXYBUTYNIN, TOLTERODINE, SOLIFENACIN AND TROSPIUM
- MANY PATIENTS BENEFIT WITH A LOW DOSE, TO FACILITATE TOLERANCE AND GRADUALLY INCREASING UNTIL MAXIMUM EFFECT IS ACHIEVED
- SIDE EFFECTS INCLUDE RETENTION, DRY MOUTH, CONSTIPATION, ETC
- NEWER DRUGS SUCH AS TOLTERODINE, TROSPIUM, SOLIFENACIN ARE MORE SELECTIVE FOR THE BLADDER(M3 MUSCARNINC RECEPTORS). HENCE LESS SYSTEMIC SIDE EFFECTS
- ANTICHOLINERGIC DRUGS SHOULD BE USED WITH CAUTION IN ELDERLY AS THERE IS AN INCREASED RISK OF DEMENTIA.THOSE WHICH DO NOT CROSS THE BBB OR HAVE A LOW PERMEABILITY SHOULD BE PREFERRED.

MANAGEMENT OF OVERFLOW INCONTINENCE (OUTFLOW OBSTRUCTION)

- ENLARGED PROSTATE (BPH) CAN BE TREATED BY DRUGS

  1. ALPHA BLOCKERS (ALFUZOSIN), TAMSULOSIN, ETC)

  2. 5-ALPHA REDUCTASE INHIBITORS (FINASTERIDE, DUTASTERIDE)

- SURGERY

MANAGEMENT OF STRESS INCONTINENCE

- PELVIC FLOOR EXERCISES (FOR WOMEN AND FOR MEN POST-PROSTATECTOMY)
- ELECTROTHERAPY ADMINISTERED BY A COMPETENT CONTINENCE NURSE
- SURGERY
- DRUG THERAPY
  1. ORAL OR TOPICAL OESTROGEN REPLACEMENT IN POST MENOPAUSAL WOMEN
  2. DULOXETINE – NOVEL AND FIRST AGENT IN THE MANAGEMENT OF URINARY STRESS INCONTINENCE

DULOXETINE

- SEROTONIN AND NORADRENALINE REUPTAKE INHIBITOR BLOCKING THE UPTAKE OF THESE NEUROTRANSMITTERS IN THE SPINAL CORD
- THIS INCREASE IN THE NEUROTRANSMITTERS STIMULATES INCREASED ACTIVITY OF THE NERVE THAT STIMULATES THE URETHRAL SPHINCTER
- CONTRACTION OF THE SPHINCTER AT THE OPENING OF THE BLADDER, PREVENTING LEAKAGE OF THE URINE DUE TO PHYSICAL EXERTION

MIRABEGRON

A NEW DRUG FOR OVERACTIVE BLADDER (URGE INCONTINENCE)-(BETMIGA,MIRBERON)

"HOW IT WORKS"

- MIRABEGRON IS THE FIRST B_3 ADENOCEPTOR AGONIST TO BE MARKETED
- IT'S LIKELY THAT MIRABEGRON EXERTS ITS EFFECTS VIA A DUAL MECHANISM BOTH DIRECTLY ON THE BLADDER SMOOTH MUSCLE AND ALSO VIA THE SENSORY NERVOUS SYSTEM
- BY STIMULATING B_3 RECEPTORS, IT INCREASES LEVEL OF CYCLIC AMP AND LEADS TO RELAXATION OF DETRUSOR MUSCLE
- MAIN ADVANTAGE IS LACK OF MUSCARINIC SIDE EFFECTS

MIRABEGRON

EVIDENCE

MIRABEGRON APPEARS TO BE MORE EFFECTIVE THAN PLACEBO IN TRIALS IN TERMS OF REDUCTION OF INCONTINENCE EPISODES AND MICTURITIONS BUT THE DIFFERENCE IS NOT STATISTICALLY SIGNIFICANT COMPARED TO TOLTERODINE

MIRABEGRON

ADMINISTRATION

- ONCE DAILY WITH OR WITHOUT FOOD
- 50mg DAILY RECOMMENDED FOR MOST ADULT PATIENTS

SIDE EFFECTS (IN TRIALS)

- URINARY TRACT INFECTION (5.9%)
- HEADACHE (4%)

MIRABEGRON

MARKETING AUTHORISATION

- AVAILABLE IN JAPAN AND US FOR OVER A YEAR
- RECENTLY REGISTERED IN UK
- SO FAR, IT APPEARS TO HAVE VERY FEW SIDE EFFECTS
- PRACTICALLY NO ANTIMUSCARINIC SIDE EFFECTS
- THE SUMMARY OF PRODUCT CHARACTERISTICS LISTS URINARY TRACT INFECTIONS AND TACHYCARDIA AS THE MOST COMMON SIDE EFFECTS (THE LATTER AFFECTING 1.2% OF PATIENTS)

MIRABEGRON

PLACE IN THERAPY

- IT IS LIKELY THAT MIRABEGRON WILL START AS AN ALTERNATIVE TO PATIENTS WHO FAIL OR CANNOT TOLERATE ANTIMUSCARINIC TREATMENT

- IT COULD BE USED FIRST LINE

- IT MIGHT ALSO BE USED IN THE FUTURE IN COMBINATION WITH ANTIMUSCARINIC (BUT FURTHER STUDIES AWAITED)

MIRABEGRON

NICE RECOMMENDS MIRABEGRON AS A POSSIBLE TREATMENT FOR SYMPTOMS OF OVERACTIVE BLADDER IN SOME PEOPLE FOR WHOM THE “ANTIMUSCARINIC DRUGS” DO NOT WORK, ARE NOT SUITABLE FOR, OR HAVE UNACCEPTABLE SIDE EFFECTS.

(TYPICALLY, 30% OF PATIENTS CANNOT TOLERATE THE SIDE EFFECTS OF ANTIMUSCARINIC DRUGS OR FIND TREATMENT TO BE INEFFECTIVE)

MISCELLANEOUS BREAKTHROUGHS

a) Expanded indications for SGLT2 inhibitors

Dapagliflozin (Forxiga), empagliflozin (Jardiance) and Canaligflozin (Invokana)

Heart failure, chronic kidney disease

MISCELLANEOUS BREAKTHROUGHS:

- BTK (Bruton Tyrosine Kinase) inhibitors – Cancer(eg ibrutinib)-targeted therapy
- CDK inhibitors (cycline dependent kinase inhibitors) – breast cancer(eg palbociclib, ribociclib)-targeted therapy
- JAK inhibitors
- Inclisiran (Leqvio) – LDL reduction
- Zolgensma (gene therapy – SMA (spinal muscular atrophy)

THE FUTURE

- Precision medicines/targeted therapies
- Biological medicines/small molecules
- ATMPs
- CNS and oncology decade
- AI/ New Technologies/ Innovations

Thank you