New & Upcoming Treatments for Adults with Alopecia Areata

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Alopecia Areata

- Relapsing Autoimmune disease
- Of Anagen hair follicles
- Worldwide incidence between 0.57% and 3.8%

Treatments

- Recently making significant strides
- We are at the beginning of new era
- HOPE & PROMISE!

Why ?

- Up to 62% of patients with alopecia areata make major life decisions including :
- Relationships
- Education
- Career based on their alopecia areata

Therapeutic Options Today

- Glucocorticoid (Steroids, Cortisone)
- - Oral
- - Topical creams & lotions
- - Intra lesional Kenalog injections

Therapeutic Options Today

- Non-Steroid Immunosuppressants ;
- Methotrexate
- Cyclosporine
- Azathioprine

JAK Inhibitors

JAK Inhibitors

- Ritlecitinib (Litfulo)

- 1st medication approved by Health Canada for AA

- Baricitinib (Olumiant)

- 1st medication approved by EMA and the Food and Drug Administration (FDA) for AA

BARICITINIB

BARICITINIB (OLUMIANT)

- The efficacy of baricitinib in alopecia areata was confirmed in two completed phase 3 randomized clinical trials (BRAVE-AA1 and BRAVE-AA2)

- 1200 patients with severe alopecia areata (SALT >50)

- At week 36, 38.8% of patients treated with baricitinib 4mg/day achieved SALT-20 compared to 22.8% of patients treated with 2mg/ day and 6.2% of patients receiving placebo.

BARICITINIB

- Recommendation :

- Baricitinib at a dose of 4mg/day

- A dose of 2mg once daily may be appropriate for patients:
- ≥75 years
- Patients with a history of chronic or recurrent infections

- A dose of 2mg once daily - patients who have achieved sustained control of disease activity with 4mg once daily

- and Eligible for dose tapering and maintenance therapy.

Side Effects (Adverse events)

- Upper respiratory tract infections
- Acne
- Nausea
- Other infections included herpes zoster and herpes simplex (3.7% of patients for each)
- but no other serious diseases were recorded
- Elevated creatine kinase levels
- Increased low- and high-density lipoprotein cholesterol levels

Different responses

- Early response was more frequent among patients :
- With severe AA (SALT score 50–94)
- Than those with very severe AA (SALT score 95–100).

- Better treatment response was noted in individuals:
- With a shorter duration of current episode of AA
- Regardless of baseline disease severity

- NON-RESPONDERS : Commonly Observed -
- Longer duration of current AA episode (≥4 years)
- Very severe AA

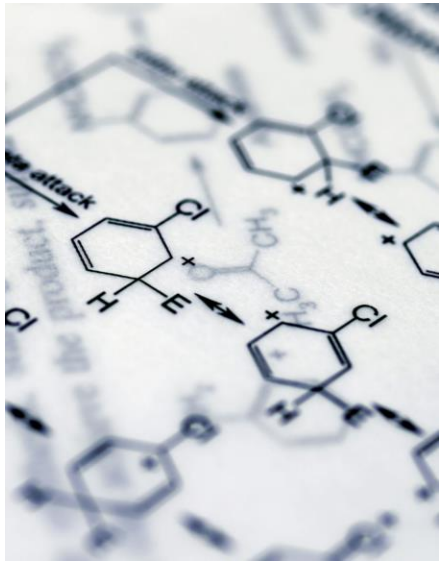
RITLECITINIB

RITLECITINIB (LITFULO)

- Ritlecitinib, a selective dual JAK3 andTYK inhibitor,

- Modulate IL-15 and IL-21 signaling and cytotoxic

- CD8+ T cells and NK cells activity



RITLECITINIB (LITFULO)

- Phase IIb/III, randomized, placebo-controlled, double-blind ALLEGRO study
- Enrolled 718 patients ≥ 12 years of age with AA causing ≥ 50% scalp hair loss
- 23% of patients treated with Ritlecitinib 50 mg daily achieved SALT ≤ 20 after 24 weeks
- Compared with 2% of patients treated with placebo.

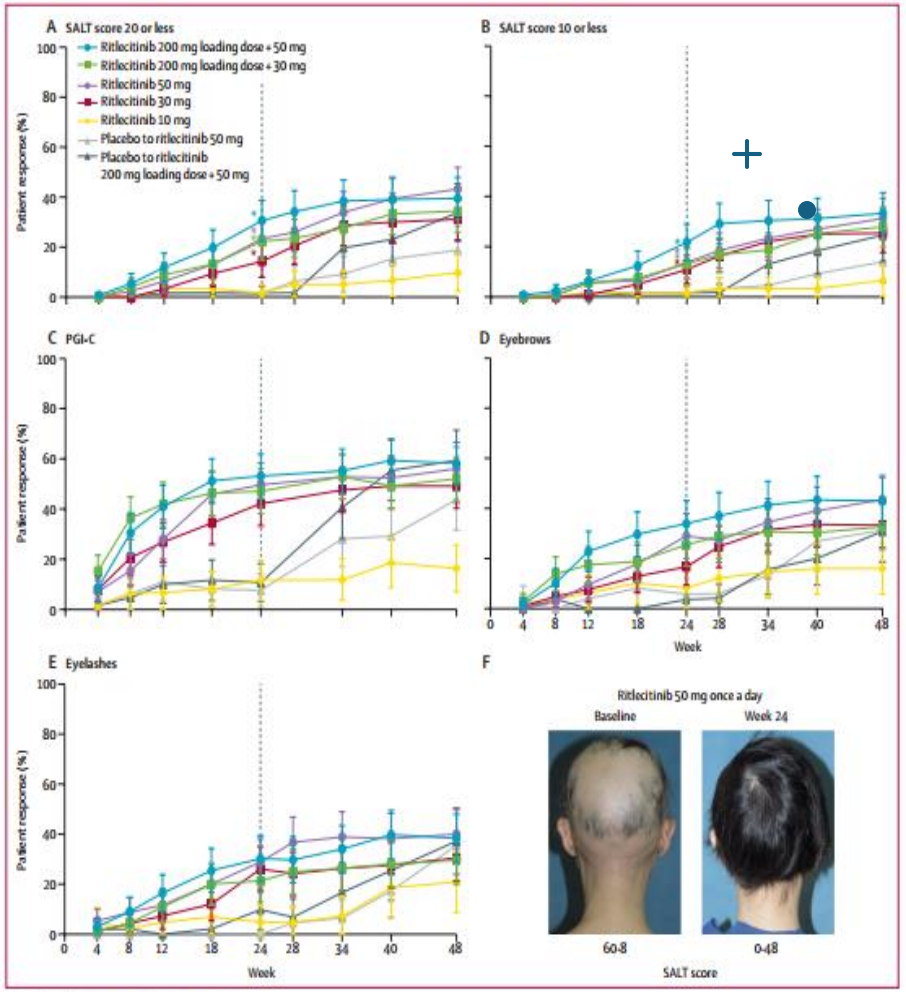


Figure 3: Patient response by treatment group
Vertical bars represent 95% CIs. (A) Response based on SALT score 20 or less. (B) Response based on SALT score 10 or less. (C) PGI-C response (score of moderately improved or greatly improved). (D) Eyebrow response (≥2 grade improvement or normal eyebrow assessment score of 3 in patients without normal eyebrows at baseline). (E) Eyelash response (≥2 grade improvement or normal eyelash assessment score of 3 in patients without normal eyelashes at baseline). (F) Representative photos of a single responder at screening and week 24. Photos from more patients are shown in the appendix (p 24). SALT=Severity of Alopecia Tool. PGI-C=Patient's Global Impression of Change. *Statistically significant versus placebo for the overall study at an overall significance level (α) of 0·05.

RITLECITINIB (LITFULO)

- Adverse events with Ritlecitinib treatment were mild:
- Upper respiratory tract infections
- Diarrhea
- Nausea
- Headaches
- Acne
- In the phase IIb/III ALLEGRO trial –
- 718 Patients enrolled :
- 8 developed Herpes Zoster
- 1 case of Pulmonary Embolism occurred
- 2 Breast cancer diagnoses were reported

BREPOCITINIB and RITLECITINIB

- Brepocitinib, a selective dual inhibitor of TYK2 and JAK1, and the selective JAK3/TEC kinase inhibitor Ritlecitinib, have been studied concurrently.

- In a phase IIa study, SALT30 was achieved by 64% and 50% of patients who received Brepocitinib and Ritlecitinib compared with placebo, respectively, while only 2% of the placebo group achieved this response

- 2 patients treated with Brepocitinib were diagnosed with rhabdomyolysis

- Recently, the crossover, open-label extension of the ALLEGRO phase IIa trial evaluating Ritlecitinib and Brepocitinib :

- Inadequate response to Ritlecitinib may benefit from shifting to Brepocitinib treatment

DEURUXOLITINIB

DEURUXOLITINIB

- Phase III clinical trial, THRIVE-AA1

- A randomized, double-blind, placebo controlled clinical trial
- 706 patients aged 18–65 years with a minimum SALT score of ≥ 50.
- 12mg and 8mg bid – both tried in initial stages

- Only 8mg now being studied now
- - Due to concern higher dose may increase risk of DVT

- Achieved SALT ≤ 20 at week 24 compared with 0.8% of patients in the placebo group

DEURUXOLITINIB

- Side effects :
- in ≥ 5% of patients treated with any dose :

- Acne
- Headache
- Upper respiratory infections
- Abnormal creatine kinase levels
- Coronavirus disease 2019 (COVID-19) infection
- Nasopharyngitis

Unique Side Effects of JAK Inhibitors

- Slightly elevated risk of DVT / Thrombosis
- Class effect
- Newer JAK Inhibitors – safer
- Patient population dependant –

❖- Age
❖- Comorbidities
❖- Other Medications
❖- Lifestyle factors

Side Effects of JAK Inhibitors

- Health Canada safety regulations for JAK inhibitors should be considered
- Discuss with your Physician
- Significant variability depending on Patient characteristics
- Case by case basis

Other agents in various studies

TOFACITINIB

- Retrospective study of Tofacitinib :
- 90 patients with AA, AT, or AU received 5 mg (or more) of Tofacitinib twice daily as monotherapy or combination therapy with prednisone
- > 5% change in SALT score
- 77% of patients achieved a clinical response rate
- 20% of patients achieved a complete response (> 90% change in SALT score)

Safety of Tofacitinib

- Common adverse effects found in AA clinical trials and observational studies :
- Upper respiratory infections
- Acne, headache
- Folliculitis
- Liver enzyme abnormalities
- Conjunctivitis

- However, the safety of tofacitinib - ?

- In 2015 :
- FDA declined the approval of Tofacitinib for moderate-to-severe plaque psoriasis due to clinical efficacy and long-term safety

Which JAK Inhibitor for which Patient

- No Head to head comparisons available
- A recent Meta-analysis found :
- Baricitinib, Ritlecitinib, & Brepocitinib appear to have equal efficacy in randomized controlled trials
- Future studies should ideally explore Personalized Clinical Medicine

IVARMACITINIB (SHR0302)

- Highly selective JAK1 inhibitor investigated for AA.
- JAK1 selectivity is hoped to have a more favorable safety profile than the pan-JAK inhibitors
- CRYSTAL2 (NCT04346316), a double-blind, randomized, placebo-controlled, phase II study :
- Statistically significant percentage change from baseline SALT scores of ≥ 25 in daily 4 and 8 mg treatment groups compared with placebo at week 24
- A phase III trial of SHR0302 (NCT05470413) - ongoing
- Safety results are consistent with profiles from previous studies of JAK inhibitors, with no incidence of major adverse cardiovascular events, deaths, or venous thromboembolism events

UPADACITINIB

- Upadacitinib, a JAK1-specific inhibitor

- Multiple case reports have shown improvement in AA symptoms in patients with concomitant AD
- In a recent retrospective cohort study involving 25 adult patients, 16% with a history of AD
- Patients were administered 15 mg/ day, with three patients increasing their dosage to 30 mg/ day after 4 weeks, for 24 weeks.

- The median SALT score decreased from 50 before treatment to 25 by week 12, and 5 by week 24
- Safety – No major concerns specific to Upadacitinib compared to other JAKI
- Herpes zoster infection
- Elevation of creatinine phosphokinase

- Malignancy, major adverse cardiovascular events, and venous thromboembolic events had similar rates across treatment groups

TOPICAL JAK Inhibitors

- Topical JAK inhibitors have fewer systemic adverse effects and may be helpful :

- Especially for specific patient populations such as Pediatrics

But

- Topical JA Inhibitors – Not meeting expectations

Topical JAK Inhibitor

- **Meta-analysis :**

- AA treated with oral JAK inhibitors Tofacitinib, Ruxolitinib, Baricitinib
- Compared to :
- Topical Tofacitinib & Ruxolitinib :

- 4 times higher odds of achieving a clinical response :
- with oral treatment versus topical

- Achieving a 50–100% Hair Regrowth vs than a 5–50% hair regrowth response
- - Oral JAK inhibitors - 7 times higher odds of response

Topical JAK Inhibitor

- Delgocitinib - a topical pan-JAK inhibitor :

- - Failed to show significant SALT improvement in a phase IIa randomized vehicle-controlled, multicentered AA study

- Ifidancitinib (ATI-502), the topical JAK1/3 inhibitor
- Failed to show significant clinical efficacy in a phase II study

TOPICAL JAK Inhibitors

- Existing evidence does not support their effectiveness
- Likely due to insufficient penetration into the deeply located hair bulb
- Several trials assessing topical JAK inhibitors have been terminated prematurely due to lack of efficacy
- A phase I/II, multicenter, randomized, placebo controlled clinical trial for topical Jaktinib is still underway

DUPILUMAB

- Th2 pathway inhibitor (IL-4 & IL-13 pathway inhibitor)

- Approved for Atopic Dermatitis, Asthma, Prurigo Nodularis….

Dupilumab

- Phase IIa clinical trial investigating the safety and efficacy of targeting the Th2 immune axis in AA patients
- Patients treated with weekly dupilumab had stabilization of hair loss compared with placebo at week 24
- 98% improvement in hair keratins at week 48 to a non-lesional state
- These results reinforce the potential role of Th2 targeting
- **For AA patients with Atopic Backgrounds**

TRALOKINUMAB

- Inhibitor of Th2 axis (IL-13 inhibitor)
- Approved for Atopic Dermatitis

- Nonetheless :
- a randomized, double-blind, placebo-controlled pilot study of 30 subjects with moderate-to-severe AA treated with either tralokinumab or placebo

- Failed to show significant clinical efficacy

Immune Checkpoint MODULATORS

Immune Checkpoint Inhibitors (ICI)

- Immune checkpoint inhibitors :
- such as CTLA-4, PD-1, and PD-L1 monoclonal antibodies

- Act by removing the inhibitory signals of T-cell activation leading to T-cell responses,

- Used in the treatment of Cancers

- Cause other Immune mediated side effects –
- - Including Alopecia Areata

Opposite if ICI – Works for AA ?

- PD-1 agonism - A promising therapeutic approach
- Reduces activated T-cell populations
- That attack the hair follicle in a collapsed IP state

Rosnilimab (ANB030)

- - Showed no dose-limiting toxicities
- Favorable profile using pharmacokinetic analysis in healthy volunteers

- Rosnilimab treatment led to a reduced number of PD-1+ conventional T (Tcon) cells,

- A phase II randomized controlled trial, AZURE, is currently enrolling patients with moderate-to-severe AA (NCT05205070).

❖**ABATACEPT**:

- CTLA4-Ig fusion protein that acts as a selective agonist of T-cell co-stimulation
- - Small series of patients
- - No ongoing active trials

❖**EQ101(BNZ-1)** (IL-9 and IL-15 Inhibition) –

- Phase II trial – currently enrolling

DAXDILIMAB

- - Monoclonal antibody targeting Ig-like transcript 7 (ILT7)
  -Inhibiting Plasmacytoid Dendritic Cells (pDCs)

- - A phase II, open-label, proof-of-concept trial of Daxdilimab for patients with AA is currently ongoing (NCT05368103)

Old, but New

1. Prostaglandin Analogues:

Latanoprost & Bimatoprost

- Maybe for Eyelash Alopecia Areata

2. IL-2 Agonism – Did not support Efficacy

3. Platelet Rich Plasma (PRP)

- More studies needed

Alopecia Areata Treatments

Hope & Promise!

Future is looking good

Important not to be deterred easily by the side effects

- Understand
- Respect the side effects
- But
- Also help understand & Re-Understand!!
- Discuss again to clarify any concerns!!

OUTCOME MEASURES
in
CLINICAL TRIALS

- Primary Outcome measure for assessment is
- - Primary end point

- **Severity of Alopecia Tool (SALT)**

Patient Reported Outcomes (PRO)

- Given the significant psychosocial burden of AA

- Other measures like Patient Reported Outcomes used
- - As Secondary end points very important

- Treatment success must also be measured by PROs

- PROs related to quality-of-life improvement and psychosocial well-being

PATIENT REPORTED OUTCOMES

- **Alopecia Areata Patient Priority Outcomes (AAPPO) questionnaire**
- **Scalp Hair Assessment PRO**
- **Alopecia Areata Symptom Impact Scale (AASIS)**

Standardization of PROs

- While several endpoints related to PROs
- &
- Clinician-reported outcome measures

- There remains a need for standardization of outcomes measures for use in clinical trials

Patient Reported Outcomes

- PROs need to have more of a say in Clinical Trial end points too
- Why ?
- Relying solely on strict guidelines, SALT 50 cut-off for severe AA
- May be insufficient
- Freedom to consider the psychological impact of the disease on their patients
- Aim for close approximation to score cut-offs when making treatment decisions.

THANK YOU!