THE USE OF IVIG IN COMBINATION WITH RITUXIMAB VS RITUXIMAB AS THE FIRST LINE TREATMENT OF PEMPHIGUS


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The use of IVIG in combination with Rituximab Vs Rituximab as the first line treatment of Pemphigus

Introduction

Pemphigus is a rare acquired autoimmune disease in which immunoglobulin G (IgG) antibodies target desmosomal proteins to produce intraepithelial, and mucocutaneous blisters. It is potentially fatal and the average mortality of pemphigus vulgaris (PV) was 75% before the introduction of corticosteroids in the early 1950s.\(^1\)

Traditionally, treatment of pemphigus included high dose systemic corticosteroids with or without adjuvant immunosuppressants.\(^1,2\) However; the prolonged use of high dose steroids carries significant side effects. A recent randomized trial has proved the efficacy of Rituximab, a monoclonal anti-CD20 antibody against B-lymphocytes, as an efficacious therapy for pemphigus.\(^3\) Furthermore,, early use of rituximab was associated with better clinical outcomes.\(^4\) Moreover, combination treatment of rituximab and intravenous immunoglobulins (IVIG) has shown to be effective for refractory pemphigus cases and can potentially induce long-term complete remission and lower risks infectious complications.\(^5-7\)

Cost effectiveness is an important issue and while combination of IVIG and rituximab has been advocated, the cost of such treatment is substantial and whether it poses any benefit over rituximab alone, or with other more conventional immunosuppressive agents, has not been established. Both treatment approaches have been previously published in high impact journals.\(^3,5\) In this study, we aim to evaluate the efficacy and safety of early use of rituximab with or without IVIG in patients with moderate to severe pemphigus using protocols that were similar to those previously published. Apart from complete remission and adverse effects, we will also aim to measure the impact of health care economics and in doing so, assess the cost and benefits of both treatment arms.

Hypothesis:

IVIG in combination with Rituximab is more superior than Rituximab alone in the treatment of moderate to severe pemphigus.
Methods:
Prospective multi-centre, randomised open-label trial
Patients will be randomised to two treatment arms: Rituximab alone or Rituximab + IVIG
Aim to recruit ~10 patients per arm (20 patients in total)
Patients will be reviewed monthly for the first 6 months then 3 monthly in clinic thereafter, follow up will be up to 4 years.

When patient enrolment is confirmed and written consent is obtained, the investigator will open the envelop sequentially and patient will receive the treatment plan stated on the allocation slip. Patient will be randomised to either rituximab arm or rituximab and IVIG arm. The random allocation sequence will be generated using computer-generated random numbers. Randomisation will be to the two arms of the trial in 1:1 ratio. The allocation sequence will be printed on paper slip. A non-study related research assistant will put the slips in to sequentially numbered, opaque, sealed envelopes.

Arm 1 (Rituximab alone arm):
- Rituximab infusion 375mg/m² body surface area (BSA) weekly for 4 weeks from baseline
- Rituximab infusion 375mg/m² BSA weekly for 4 weeks at week 24
- Rituximab infusion 375mg/m² BSA weekly for 4 weeks at week 52
- A total of 12 doses of rituximab will be given in 55 weeks
- If a patient relapses after initial rituximab infusion, further rituximab infusion 375mg/m² BSA weekly for 4 weeks can be given at time of relapse/or if patient fails to achieve complete remission 2 months from last dose of rituximab.

<table>
<thead>
<tr>
<th>Week 0, 1, 2, 3</th>
<th>Rituximab (375mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24, 25, 26, 27</td>
<td>Rituximab (375mg/m²)</td>
</tr>
<tr>
<td>Week 52, 53, 54, 55</td>
<td>Rituximab (375mg/m²)</td>
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</tbody>
</table>

Arm 2: (Rituximab and IVIG arm):
- Rituximab (375 mg/m² BSA) once a week for 4 weeks (week 1, 2, 3) and
- Week 4: Rituximab + IVIG 2g per kg
- Week 5, 6, 7: Above treatment repeated for 2nd cycle, infusion of rituximab (375 mg/m² BSA) once a week for 4 weeks (week 5, 6, 7) and
- Week 8: Rituximab + IVIG 2g/kg
- In week 12, 16, 20, 24 patients received a single infusion of rituximab (375 mg/m² BSA) plus infusion of 2g/kg IVIG
- Thus in 24 week period patients received a total of 12 infusions of rituximab and 7 infusions of IVIG
- If a patient was clinically free of disease at end of 24 weeks, additional infusions of IVIG will be given at week 30, 38, 48, 60 and 76
- A total of 12 doses of rituximab will be given and 12 cycles of IVIG will be given
- If a patient relapses or flares during the treatment, four infusions of rituximab at 375mg/m² BSA will be given at 1-weekly interval will be administered and IVIG 2g/kg will be given at week 4 of treatment after week 32
Week 0  IVIG 2g/kg, divided total dose given over 2-5 days
Week 1, 2, 3  Rituximab (375mg/m²)
Week 4  Rituximab (375mg/m²) + IVIG
Week 5, 6, 7,  Rituximab (375mg/m²)
Week 8  Rituximab (375mg/m²) + IVIG
Week 12  Rituximab (375mg/m²) + IVIG
Week 20  Rituximab (375mg/m²) + IVIG
Week 24  Rituximab (375mg/m²) + IVIG
Week 30  IVIG
Week 38  IVIG
Week 48  IVIG
Week 60  IVIG
Week 76  IVIG

For both study arms:
- After initial induction phase for both arms, the time between subsequent doses of rituximab for treatment of relapse should be at least 2 months apart.
- Patients will be followed up for 4 years starting from baseline visit

**IVIG and Rituximab**

Ahmed et al.\(^5-7\) has published data and protocol combining rituximab and IVIG. The theory behind this is that IVIG:
- Contains antibodies directed against B-cell-activating factor belonging to tumour necrosis family
- Exact mechanism by which Rituximab and IVIG are effective in induction of prolonged sustained clinical, serological and immuno-pathological remission in patients is not clearly understood – After destroying autoantibody-producing pathogenic B cells, the repopulating B cells do not produce autoantibodies. It is conceivable that in a microenvironment that more closely resembles normal physiology and homeostasis, IVIG could initiate the process of immune restoration.

**Current practice/treatment in local hospital (IVIG +Rituximab) and existed side effects**

IVIG and rituximab combination therapy has not been used in local hospitals for the treatment of pemphigus. This is a pilot study in Hong Kong comparing the use of combination therapy with IVIG and Rituximab versus rituximab alone in the treatment of pemphigus. Ahmad et al.\(^8\) found that combination therapy with IVIG and rituximab in 10 patients with pemphigus with contraindications to systemic corticosteroid resulted in long-term sustained remission (> 6 years). Of note there were lack of adverse events, no infections, deaths or hospitalisations.
Criteria:

Ages Eligible for study: 18 years to 70 years (Adult, Older Adult), by the day of signing informed consent

Sexes Eligible for study: All

Inclusion Criteria:

- Written informed consent obtained from patient
- Ages Eligible for Study: 18 years to 70 years (Adult, Older Adult)
- Newly or recently diagnosed (less than 18 months) diagnosed pemphigus vulgaris or pemphigus foliaceus based on clinical features; histological features of acantholysis via skin or mucosal biopsy; and intercellular staining pattern of indirect immunofluorescence or serological detection of DSG 1 or DSG 3 by enzyme-linked immunosorbent assay (ELISA)
- Moderate to severe active disease, as defined by overall PDAI >= 15 or skin involvement BSA>= 5% [Annex 1]
- Receiving standard-of-care oral prednisolone up to 1.5 mg/kg/day
- Women who are sexually active and not postmenopausal, agreement to remain abstinent or use 2 effective methods of contraception.
- Ability to comply with study protocol as deemed by investigator’s assessment

Exclusion criteria:

- Age <18 or >70
- Pregnant women or nursing mother
- Already diagnosed pemphigus patients diagnosed > 18 months
- Non-consenting patients, or patient who cannot be followed up regularly
- Patient with history of serious allergy or anaphylactic reaction to monoclonal antibody treatment
- Severe heart failure (NYHA Class III or IV)
- Unstable angina or myocardial infarction within last 3 months or post-infarction heart failure
- Anaemia (haemoglobin <10g/dL), Neutropenia (<1000/mm³), Lymphopenia (<900/mm³), thrombocytopenia (<100,000/mm³)
- Renal insufficiency eGFR <60
- Liver insufficiency of ALT/ALT > 2 times normal limit range
- Positive test results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C (HCV) serology at screening
- Blood test positive for HIV
- Signs of active infection on CXR
- Positive interferon gamma release assay Quantiferon or T.Spot TB test: must be treated with at least 4 weeks post initiation of isoniazid or other TB therapy
- Inherited or acquired severe immunodeficiency
- History of malignancy
- Patient with active severe infection (excluding fungal infections of the nail), which has required antibiotic treatment within 2 week prior to study enrolment
Rituximab protocol version 4.0 (29.04.2020)

- Infection requiring hospitalisation or intravenous antibiotic treatment within the last 8 weeks prior to enrolment
- Past history of osteomyelitis, or fasciitis, septic arthritis within the last one year
- Patients with drug induced pemphigus. A thorough medication history will be taken to rule out drug induced pemphigus including D-penicillamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and cephalosporins
- Evidence of any new or uncontrolled concomitant disease that in the investigators’ judgement would preclude the patients participation
- Patients with history of allergy or adverse events to IVIG or rituximab treatment
- Treatment with intravenous immunoglobulins, plasmaphoresis within the last 8 weeks prior to randomization
- Previous treatment with rituximab or any monoclonal antibody inducing profound lymphopenia
- Treatment with live or attenuated vaccine within the last 28 days prior to randomization

**Admission and follow up:**
- All infusions will be performed as in-patient procedure of prospective hospital and all patients are to be follow up monthly at out-patient of the prospective Queen Mary Hospital dermatology out-patient clinic
- Patients will be followed up monthly for the first 6 months, then followed up for every 3 months up to 4 years starting from baseline visit
Outcome measures:

Patients’ serum will also be taken for desmoglein antibodies and levels will be charted and independent samples t-test will be used to compare the collected data between the two groups. Homogeneity of the treatment groups at baseline will be analyzed using the Mann–Whitney U test and Wilcoxon signed-rank test for independent and dependent variables. The Kaplan-Meier method will be used to estimate the likelihood of reaching the endpoint of relapses or flares within the drug infusing period based on the intention-to-treat population, defined as all patients who has received at least one dose of study medication. The log-rank test will be used to compare time-to-event curves between treatment groups.

Statistical analysis of results will be done with IBM SPSS statistic program version 25. All tests of significance are two-tailed, and a P value of < 0.05 is considered to indicate statistical significance.

Primary outcome:
1) Percentage of participants who achieve relapse-free complete remission

Secondary Outcomes:
2) Time to protocol defined disease flare
3) Duration of complete remission, evaluated by the PDAI activity score [Baseline up to end of study]
4) Number of protocol defined disease flares
5) Time to initial complete remission, evaluated by the PDAI activity score [Baseline up to end of study]
6) Change in health-related quality of life as measured by the Dermatology Life Quality Index (DLQI) Score [Time Frame: Baseline, Week 12, 24, 36, 48, 60, 72, 84, 96, 104]
7) Occurrence of severe treatment adverse events (grade 3 or 4) based on common terminology criteria for adverse events (CTCAE), or death from any cause Blood DSG 1 and 3 levels [Baseline week 0, week 4, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192]
8) Blood lymphocyte level (CBC) [Baseline week 0, week 4, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192]
9) Blood CD19/20 mean B cell counts percentage [Time Frame: Baseline, week 4, 24, 36, 48, 60, 72, 96, 120, 144, 168, 180, 192]
10) Number of rescue therapy given

Baseline investigations prior to commencing therapy

General investigations:
- CBC
- Renal panel
- Liver panel
- Fasting Glucose/HbA1c
- Urine microscopy
- Urine pregnancy test in women of childbearing age
- Serum immunoglobulins for IgA deficiency
- B cell (CD19/20) enumeration
- DSG 1, 3 ELISA

Infective screen:
- HepBs Ag, Anti-HBs Ab, anti-HepBc total antibodies
- Anti-HCV IgG
- Anti HIV 1 and 2 (if indicated)
- CXR
- Interferon-gamma release assays

As Tuberculosis (TB) is endemic in Southeast Asia, should Interferon-gamma release assays result be positive, the patient will be reviewed by infectious diseases specialist and need treatment of latent TB treatment prior to starting Rituximab. Patients will need to have completed at least 4 weeks of isoniazid or treatment with other TB medications, before commencement of study.
Monitoring and definitions of disease outcome parameters:

- **Control of disease activity**: Time at which new lesions cease to form and established lesions begin to heal.
- **End of consolidation phase**: Time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed.
- **Complete remission**: The absence of new or established lesions.
- **Complete remission off therapy**: The absence of new or established lesions while the patient is off all systemic therapy for at least two months.
- **Relapse/flare**: Appearance of >= 3 new lesions/month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control.

Steroid regimen and tapering:

Prednisolone tapering

Severe Pemphigus (PDAI >=45):  
- Prednisolone 1mg/kg/day for 1 month, then 0.75mg/kg/day for 1 month then 0.5mg/kg/day for 1 month, then 0.3mg/kg/day for 1 month then 0.2kg/mg/day for 1 month, then 0.1mg/kg/day for 1 month then off.

Moderate pemphigus (PDAI >=15):  
- Prednisolone 0.5mg/day/day for 1 month, then 0.3mg/kg/day for 1 month then 0.2mg/kg/day for 1 month then off.

Steroid sparing agents such as azathioprine or MMF are reduced to half the dose once the patient is successfully recruited into the study and will be tapered and stopped upon commencement of the study.

Relapse/ failure to achieve complete remission

- Additional infusion of weekly rituximab 375mg/m2 BSA weekly x 4 will be given at the time of relapse/ or if patient fails to achieve complete remission 2 months from last dose of rituximab. After initial induction phase for both arms, the time between subsequent doses of rituximab for treatment of relapse should be at least 2 months apart.

Rituximab infusion protocol:

Pre-medications
- Paracetamol 1000mg one hour before Rituximab infusion
- IV Piriton 30 minutes before Rituximab infusion
- Methylprednisolone 100mg IV or Hydrocortisone 100mg IV half hour before Rituximab infusion

Preparation:
- IV Rituximab is prediluted at a dose of 500mg in 500ml of 0.9% normal saline (i.e. 1:1 dilution, 1 mg/ml)
- Initial infusion rate starts at a rate of 50mg/hr (50ml/hr)
- If no hypersensitivity/anaphylaxis reaction occurs, increase infusion rate in 50mg/hr (50 ml/hr) increments every 30 minutes
- Maximum infusion rate is 400 mg/hr (400 ml/hr)
- Subsequent infusion: start at rate of 100mg/hr (100 ml/hr), increase 100mg/hr (100 ml/hr) increments every 30 minutes
- Monitor temperature, BP HR, respiratory rate and SpO2 every 30 minutes

Adverse effects

Infusion-related:
- Fever, chills/rigors
- Injection site pain
- Nausea and vomiting
- Asthenia, headache, myalgia, giddiness
- Rhinitis, throat irritation
- Pruritus, rash
- Risk of infections
  ** Infections including urinary tract infections, pneumonia, pneumocystic pneumonia, herpes simplex, herpes zoster, cytomegalovirus infection. Lung and brain abscess. Severe hypogammaglobulinaemia, and high-dose immunosuppressants may be possible risk factors for systemic infections
- Neutropenia
- Pyelonephritis
- Haemolytic anaemia
- Toxic epidermal necrolysis
- Parkinsonism

Intravenous immunoglobulins (IVIG)
Treatment dosage: 2g/kg over 2-5 days

Infusion Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>50ml/hour</td>
</tr>
<tr>
<td>15 min</td>
<td>75ml/hour</td>
</tr>
<tr>
<td>30 min</td>
<td>100ml/hour</td>
</tr>
<tr>
<td>45 min</td>
<td>125ml/hour</td>
</tr>
<tr>
<td>60 min</td>
<td>150ml/hour</td>
</tr>
<tr>
<td>75 min &amp; beyond</td>
<td>180ml/hour</td>
</tr>
</tbody>
</table>

For patients receiving IVIG for first time, wait 30mins before 1st increase. Infusion rate should be less than 0.27ml/kg/hour in the following groups of patients:

- Renal insufficiency
- Diabetes mellitus
- >=65 years of age
- Sepsis
- Paraproteinaemia
- Patients receiving nephrotoxic drugs

* In patients with renal impairment, or risk factors for thromboembolic disease or fluid overload, consider infusing IVIG at a dose of 0.4g/kg/day for 5 days (total dose 2g/kg) at a rate of less than 0.27ml/kg/hour, and in not less than 8 hours.
• Restoring immune regulation when B cells are being re-populated to normal levels
• Synergy and interactions of immune pathways and inflammatory system
• IVIG regulated B cell functions and suppression of production of pathogenic autoantibodies through idiotype network interactions

**During IVIG infusion:**

• Hourly parameters, watch out for tachycardia, hypertension, dyspnoea, chest tightness, facial flushing, fluid overload
• In the event of an adverse reaction:
  - Inform the doctor
  - Decrease the infusion rate to previous level or stop the infusion if symptoms persist
  - Do not increase the rate any further
  - Paracetamol for fever, chills, headache or myalgia and antihistamines for pruritus or urticaria
  - Restart at a slower rate when symptoms have resolved, and consider premedication prior to future infusions
  - Report as adverse reaction to a blood product

**Anaphylactic reaction**

Syncope (dizziness), dyspnoea, hypotension

• Stop the infusion immediately
• Resuscitate if necessary
• Oxygen therapy, IV antihistamines (benadryl 50mg) and other appropriate measures

**Other potential adverse events:**

• Acute renal failure
  Elderly patients and those with diabetes mellitus or impaired renal function are at risk

• Arterial thrombosis (stroke and myocardial infarction) and venous thrombosis (deep vein thrombosis and pulmonary embolism) following IVIG have been reported. Patients at risk of thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity.6

• Transmission of blood-borne agents such as Hepatitis B/C and HIV

• Acute meningitis syndrome
  This may occur 48 to 72 hours after IVIG.
  Signs and symptoms include severe headache, nuchal rigidity, drowsiness, fever, photophobia, nausea and vomiting.
  May occur more frequently with high dose (2g/kg) IVIG treatment.
Cutaneous reactions
Reports of eczematous reactions and other varied morphologies. One report of erythema multiforme.

The British Associate of Dermatologists guidelines for management of pemphigus vulgaris 2017

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral prednisolone 0.5-1mg/kg</td>
</tr>
<tr>
<td></td>
<td>Increase 50-100% increments every 5-7 days if blistering continues</td>
</tr>
<tr>
<td></td>
<td>Taper dose once remission is induced and maintained</td>
</tr>
<tr>
<td></td>
<td>Assess risk of osteoporosis</td>
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<tr>
<td>Combine corticosteroids with an adjuvant immunosuppressant</td>
<td></td>
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<tr>
<td>Rituximab (rheumatoid arthritis protocol, 2x 1g infusions, 2 weeks apart)</td>
<td></td>
</tr>
<tr>
<td>Azathioprine 2-3 mg/kg per day (if TPMT normal)</td>
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</tr>
<tr>
<td>Mycophenolate mofetil 2-3g/day</td>
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</table>

| Second-line therapy | Consider switching to alternate corticosteroid-sparing agent if treatment failure with first-line adjuvant drug (azathioprine, mycophenolate mofetil or rituximab) |

| Third-line therapy | Consider additional treatment options based on assessment of individual patient need and consensus of multidisciplinary team, options include: |
|                   | Cyclophosphamide |
|                   | IVIG |
|                   | Methotrexate |
|                   | Plasmapheresis or plasma exchange |

Additional management for oral pemphigus

- Topical analgesics or anaesthetics (e.g. viscous lidocaine 2% solution, lidocaine 2% gel, difflam gargle) are useful particularly prior to eating or toothbrushing
- Topical medium or high potency corticosteroids (e.g. triamcinolone acetonide 0.1% in adhesive paste, clobetasol propionate) applied directly to the lesions, corticosteroid mouthwashes are more practical for multiple oral erosions
- Topical calcineurin inhibitors (e.g. tacrolimus 0.1% ointment) and topical cyclosporine swish and spit may be beneficial
- Candida infection is a common occurrence in patients with mucosal pemphigus who are treated with systemic glucocorticoids. Oral nystatin swish and swallow/spit can be given as prophylaxis. Alternatively, patients can be monitored closely for the development of oropharyngeal candida infection and treatment instituted if infection develops.
- Dietary advice: soft diet, avoidance of spicy/very hot foods
• Maintenance of good oral hygiene: antiseptic mouthwashes (e.g. chlorhexidine 0.2% gluconate), teeth should be brushed twice daily with a soft-bristle brush and a bland toothpaste, flossing daily, regular dental consultations
• Nutritional management with the help of a dietician or a nutritionist if malnutrition is related to oral involvement

**Patient consent**

The participation is voluntary, Patient can withdrawal consent at any time without affecting his/her usual management. Patients will be informed about the potential risks and benefit of these procedures. Patient will be given sufficient time to consider and ask questions before signing the informed consent to join the trial.

**Insurance**

An insurance policy under the HKU Master clinical Trial Insurance Policy has been issued and the policy provides no-fault coverage for claims related to the study design in the adverse effects arising from the investigational products and interventions used in accordance with the study protocol.

Confidentially

All study documents will be stored in a locked environment or with password-protected, separate from clinic setting and will only be assessable by the authorized study personnel or regulatory authorities. The PI will be responsible for the safekeeping of personal data during and after the study for up to 15 years upon study completion.

**Declaration**

The study will be conducted in compliance with Declaration of Helsinki and ICH-GCP guidelines.
References:


### Annex 1

**Pemphigus disease area index (PDAI)**

<table>
<thead>
<tr>
<th>Skin Anatomical Location</th>
<th>Activity</th>
<th>Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erosion/Blisters or new erythema</td>
<td>Post-inflammatory hyperpigmentation or erythema from resolving lesion</td>
</tr>
<tr>
<td>0</td>
<td>absent</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1–3 lesions, up to one &gt;2 cm in any diameter, none &gt; 6 cm</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3–10 lesions, at least two &gt; 2 cm diameter, none &gt; 6 cm</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;3 lesions, none &gt; 6 cm diameter</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;3 lesions, and/or at least one &gt;6 cm</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&gt;3 lesions, and/or at least one &gt;6 cm diameter of entire area</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ears</th>
<th>Nose</th>
<th>Rest of the face</th>
<th>Neck</th>
<th>Chest</th>
<th>Abdomen</th>
<th>Back/shoulders</th>
<th>Arms</th>
<th>Hands</th>
<th>Legs</th>
<th>Feet</th>
<th>Genitals</th>
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</table>

<table>
<thead>
<tr>
<th>Total skin</th>
<th>/120</th>
<th>/12</th>
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</table>

<table>
<thead>
<tr>
<th>Scalp</th>
<th>Erosion/Blisters or new erythema</th>
<th>Number lesions if x 3</th>
<th>Post-inflammatory hyperpigmentation or erythema from resolving lesion</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>absent</td>
<td>0</td>
<td>absent</td>
</tr>
<tr>
<td>1</td>
<td>in one quadrant</td>
<td>1</td>
<td>present</td>
</tr>
<tr>
<td>2</td>
<td>two quadrants</td>
<td>2</td>
<td>present</td>
</tr>
<tr>
<td>3</td>
<td>three quadrants</td>
<td>3</td>
<td>present</td>
</tr>
<tr>
<td>4</td>
<td>affects whole skull</td>
<td>4</td>
<td>present</td>
</tr>
<tr>
<td>5</td>
<td>at least one lesion &gt; 6 cm</td>
<td>5</td>
<td>present</td>
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<table>
<thead>
<tr>
<th>Total Scalp</th>
<th>/10</th>
<th>/1</th>
</tr>
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<table>
<thead>
<tr>
<th>Vucous Membrane Anatomical Location</th>
<th>Erosion/Blisters</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>absent</td>
</tr>
<tr>
<td>1</td>
<td>1 lesion</td>
</tr>
<tr>
<td>2</td>
<td>2–3 lesions</td>
</tr>
<tr>
<td>3</td>
<td>&gt;3 lesions or 2 lesions &gt; 2 cm</td>
</tr>
<tr>
<td>4</td>
<td>entire area</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Total Vucous Membrane</th>
<th>/120</th>
<th>Total Damage Score</th>
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**Additional notes:**