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Indonesian clinical practice guidelines for systemic and biologic agents for adults with plaque psoriasis

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Abstract

Background: In response to various biologic and non-biologic systemic agents available in Indonesia, proper and accredited treatment guidelines are required to ensure patient safety. Appropriate treatment is crucial and may affect remission time and morbidities. These guidelines were developed by the Indonesian Society of Dermatology and Venereology – *Kelompok Studi Psoriasis Indonesia* (INSDV-KSPI) to provide updated decision-making algorithms for the biologic and non-biologic systemic agents for the treatment of adult patients with plaque psoriasis.

Methods: Experts from twelve institutions across Indonesia were involved in developing the guidelines. Subsequently, a focus group discussed various journals, researchable questions, eligibility criteria, and outcomes of various treatments options.

Results: Modified evidence to decision framework of treatment choices were constructed to aid dermatovenerologists across Indonesia in making a clinical judgment on the size of treatment options of biologic and non-biologic systemic agents for psoriasis treatment in Indonesia.

Conclusion: These clinical practice guidelines, accepted and acknowledged by the Indonesian Society of Dermatology and Venereology - *Kelompok Studi Psoriasis Indonesia (INSDV-KSPI)*, have been developed to present the latest and concise evidence- and experience-based guideline targeted towards dermatovenereologists in Indonesia on the management of adult plaque psoriasis.

Keywords: *biologic agents, guidelines, Indonesian, psoriasis*

Abbreviations used:

AS	: Ankylosing Spondylitis
BSA	: Body Surface Area
BPJS	: <i>Badan Penyelenggara Jaminan Sosial</i>
CBC	: Complete Blood Count
COVID	: Coronavirus disease
CRP	: C-Reactive Protein
CsA	: Cyclosporine A
DLQI	: Dermatology Life Quality Index
IBD	: Inflammatory Bowel Disease
MTX	: Methotrexate
NAFLD	: Non-Alcoholic Fatty Liver Disease
JKN	: <i>Jaminan Kesehatan Nasional</i>
PASI	: Psoriasis Area Severity Index
PSO	: Psoriasis
PsA	: Psoriasis Arthritis
PUVA	: Psoralen Ultra Violet A
TB	: Tuberculosis

Background

Psoriasis is a chronic skin inflammatory condition with a genetic disposition characterized by epithelial growth and differentiation abnormalities, with an increased risk of painful and destructive arthritis.¹ The number of psoriasis visits has been growing in many regions, resulting in a substantial psychosocial burden of psoriasis in Indonesia.²

Indonesia is a highly populated country with 267 million of population. In 2018, six teaching hospitals in Indonesia reported 177 new cases and 4,230 cases of plaque psoriasis in the outpatient dermatology clinics. The number of hospital visits of patients with psoriasis between cities varied. The city with the highest new case

was Yogyakarta, with 64 new cases and 1,858 visits of psoriasis vulgaris patients in 2018, with Semarang with the lowest hospital visits (0 new cases and 76 old cases of hospital visits).

Psoriasis vulgaris or plaque psoriasis is a chronic inflammatory skin disorder characterized by well-demarcated red plaques with silvery scales, mainly involving the scalp, elbows, knees, and presacral region. Psoriasis may also involve other skin areas such as soles, palms, nails, and genitalia.^{1,3}

The severity of psoriasis is determined by the total body surface area (BSA) affected by the disease. The involvement of less than or equal to 3% of BSA is considered mild, involvement of greater than 3% to 10% of BSA is considered moderate, while the disease is deemed to be severe if any of the following features is present: the involvement of BSA greater than 10%, any presence of comorbidities, recalcitrance to treatment, and/or the involvement of certain locations; including but not limited to, the nail, hands, feet, scalp, face, or genital (on which psoriasis may be difficult to treat). (Figure 1)^{3,4}

The Psoriasis Area Severity Index (PASI) is a more specific tool for calculating the extent and severity of psoriasis, which takes not only the affected BSA into account, but also the intensity of redness, scaling, and plaque thickness. PASI generates a score interval from 0 (no disease) to 72 (maximal disease severity).

It is commonly used to monitor the response of psoriasis treatments and determine the severity of psoriasis.³

Pathogenesis of psoriasis involves skin-resident T cells, dendritic cells, and keratinocytes, with subsequent release of various cytokines and other soluble mediators responsible for keratinocyte hyperproliferation, manifesting as scaly plaques. These cytokines and mediators may also contribute to the augmented inflammation underlying several associated systemic diseases, such as metabolic syndrome, cardiovascular disease, and psoriatic arthritis (PsA).^{1,3}

To inhibit the inflammatory process underlying this condition, broad-spectrum treatment consisting of topical and systemic medications are available. Upon choosing the treatment regimen, the measurable severity and patient's safety of long-term use of psoriasis treatment is important to consider.³ Based on the continuous progress in research regarding psoriasis and advances in molecular biology, biologic agents specifically designed to block certain pathogenic pathways of psoriasis have emerged.^{1,3} Biologic agents are defined as antibodies and proteins engineered from living organisms that induce or alter immune responses by interacting with specific biologic targets that exert their therapeutic actions by blocking specific cytokines or cytokine receptors critical to psoriasis inflammation.⁵ They consist of recombinant cytokines, growth factors, fusion protein, monoclonal antibodies, which may be fully human, humanized, or chimeric. Currently, three types of biologic agents have been approved by the Indonesian National Agency of Drug and Food Control.^{3,5}

Due to the uncertainty in previous consensus and the need to determine

sufficient information available for physicians for such treatments, and considering the availability of systemic treatment in Indonesia, we conducted a focus group discussion to define a proper and accredited guideline of biologic and nonbiologic systemic agents use for adult plaque psoriasis treatments in Indonesia.

This guideline aimed to propose updated decision-making algorithms for dermatovenerologists to treat adult patients with plaque psoriasis. The new algorithms were developed based on the current scientific data and the emergence of highly effective new drugs to treat psoriasis, fulfilling the National Health Insurance (JKN) program held by the Healthcare and Social Security Agency (BPJS).

Methods

These revised and updated guidelines for biologic and nonbiologic systemic agents were established according to Oxford Centre for Evidence-based Medicine (2011). The criteria for therapeutic level of evidence is presented in Table 1.^{6,7}

Twenty-two experts from 14 institutions all across Indonesia were invited to a focus group discussion in Jakarta, held on April 21st, 2019. First, we conducted literature research, relevant outcomes, and data to discuss relevant addition to the current guidelines. Effect measures, such as risk ratios expressing the size of an effect, from the literature were thoroughly discussed. During the focus group discussion, all participants accepted the proposed recommendations. The discussion followed a structured approach: presentation of evidence, the draft recommendation as defined in Table 2, discussion, and final agreement. All consented recommendations are further presented as algorithms below.

Table 1. Level of evidence (LoE) criteria of therapy

Level of Evidence	Criteria
1	A Systematic review of randomized trials or n-of-1 trials
2	Randomized trial or observational study with dramatic effect including crossover study
3	Non-randomized controlled cohort/follow up study
4	Individual case-control study
5	Case-series, case-control, or historically controlled studies
	Mechanism-based reasoning

Source: Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence⁶

The grade of recommendation used in Indonesia's practical guidelines for dermatovenereologists is modified from the European Society for Clinical Microbiology and Infectious Disease, 2016.^{6,7}

Table 2. Criteria for the grade of recommendation

Strength of Recommendation	European Society for Clinical Microbiology
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use

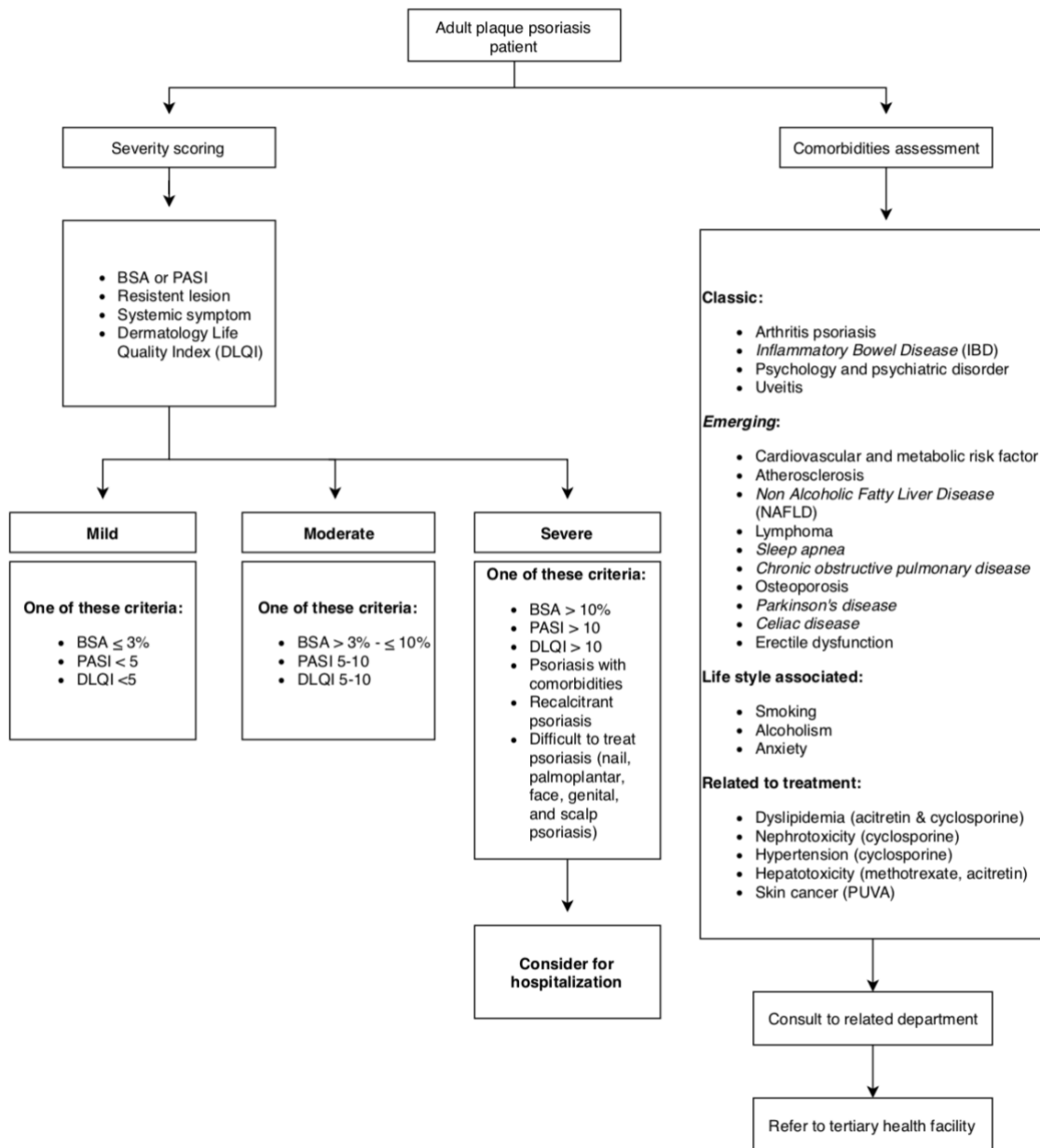
Source: Oxford Centre for Evidence-based Medicine Levels of Evidence⁶

Table 3. The half-life of biologic agents³

Biologic Agents	Approximate half-life (days)
Etanercept	3.5
Infliximab	10
Adalimumab	14
Ustekinumab	21
Secukinumab	27
Guselkumab	18

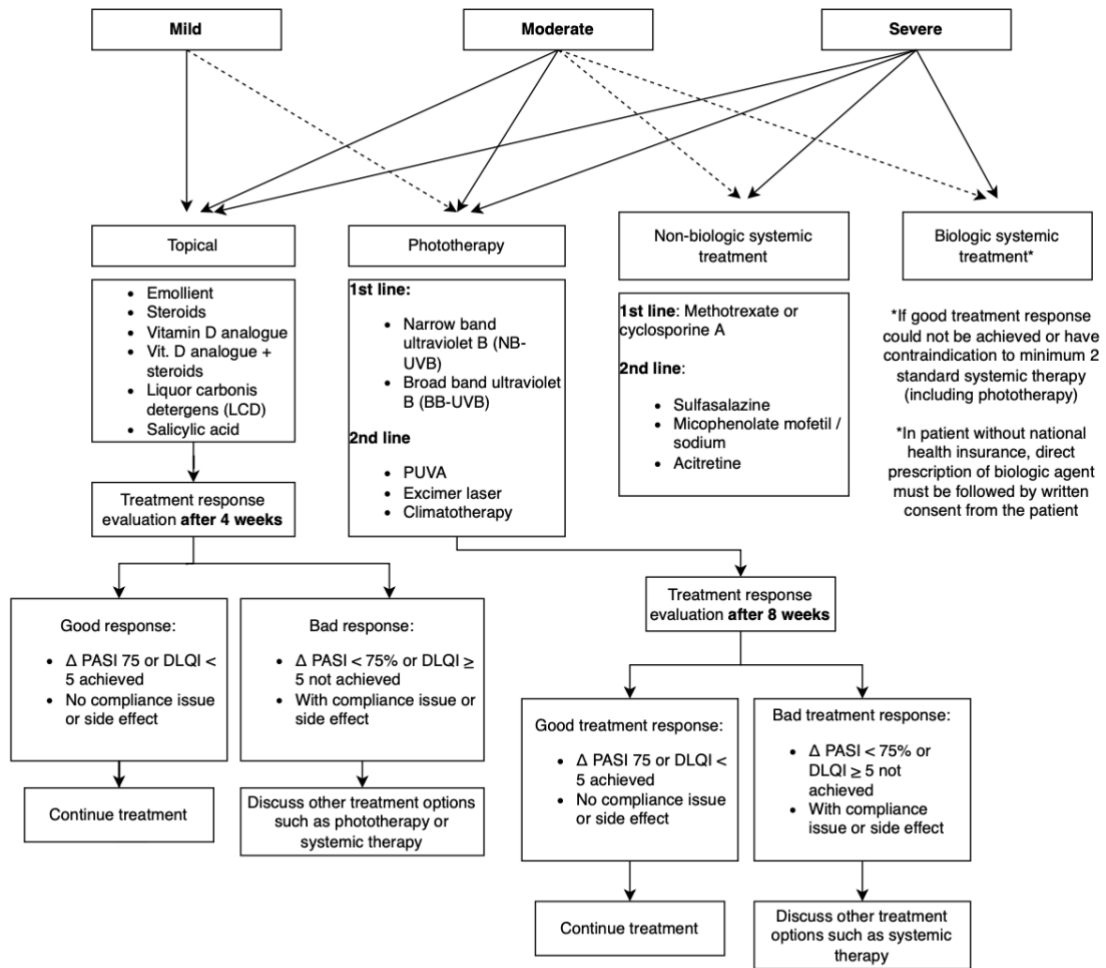
Results

Figure 1. Classification of plaque psoriasis (adult)^{1,3,4,7,10,11-14}



Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 2. Algorithm of plaque psoriasis in adult (A,1)^{1,3-5,7,10,11-14}



Notes :

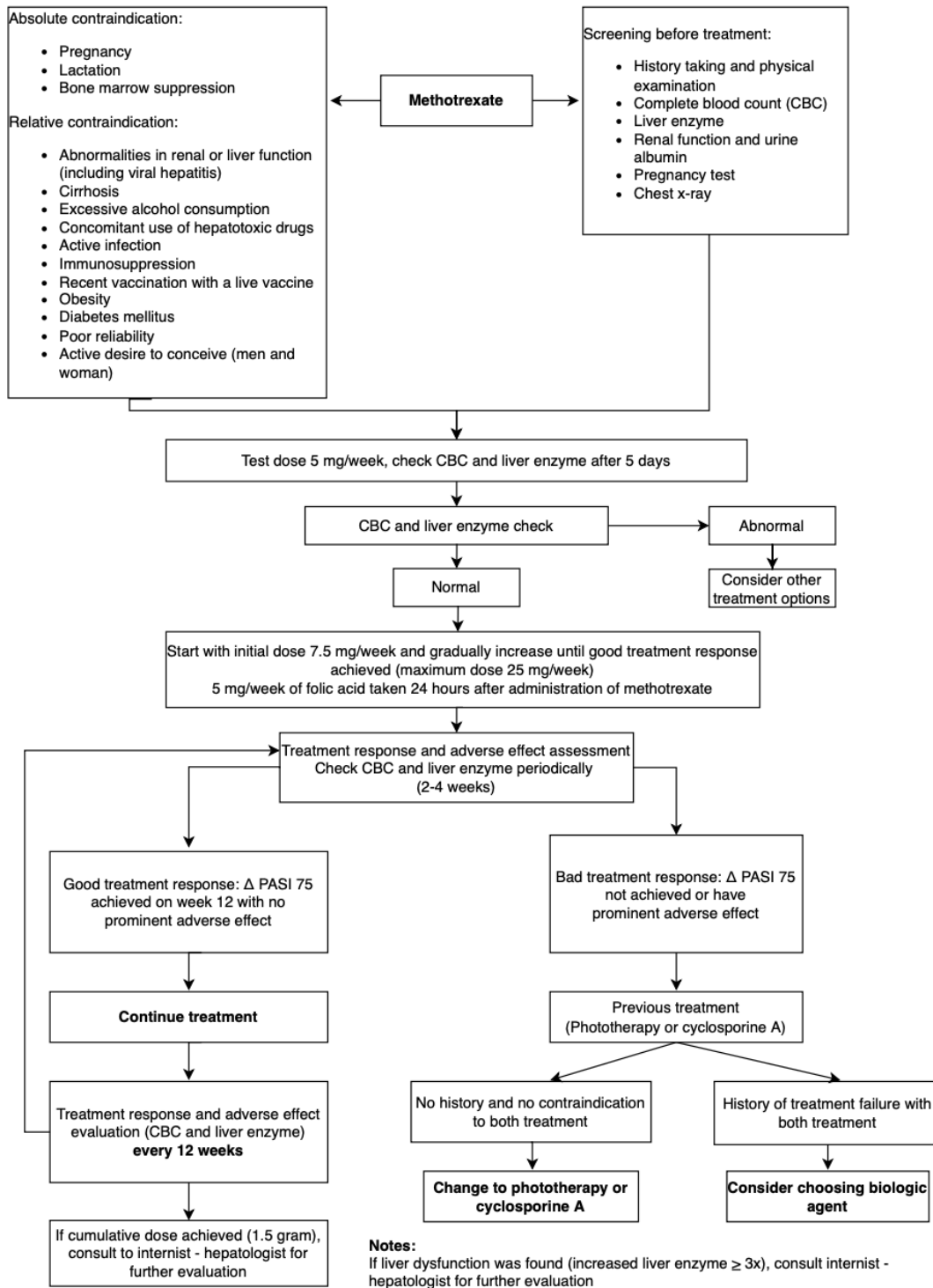
- PASI score could be assessed manually or using application.
- Δ PASI 75 is defined as 75% improvement of psoriasis area and severity index from baseline
- If the drug is not available, the patient could be referred to higher health care facility
- Phototherapy, non-biologic systemic treatment, and biologic treatment could only be prescribed by dermatovenereologist

Description:

- Choice of treatment
- Alternative treatment

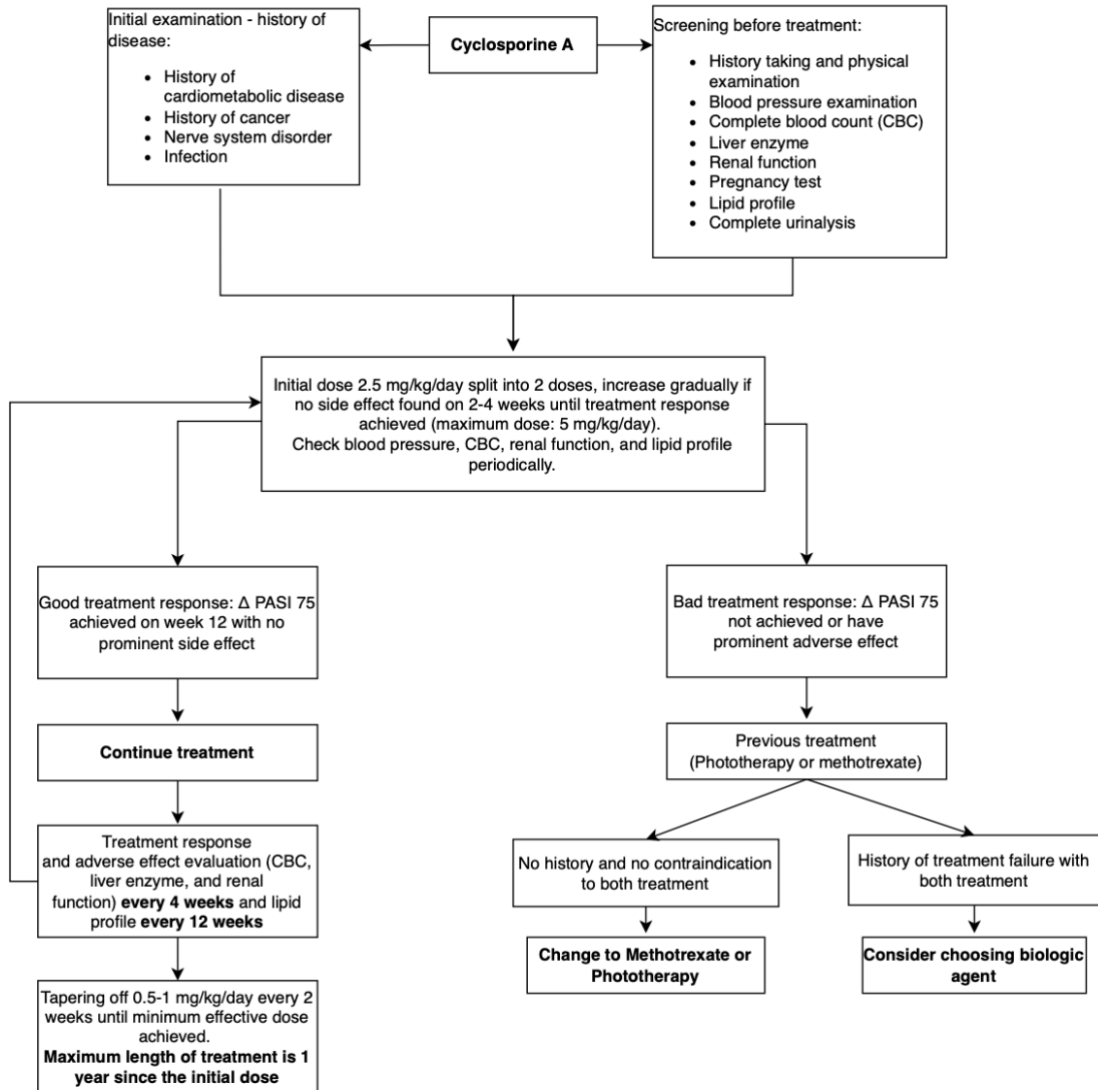
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 3. Methotrexate algorithm (A,1) ^{1,3,7-14}



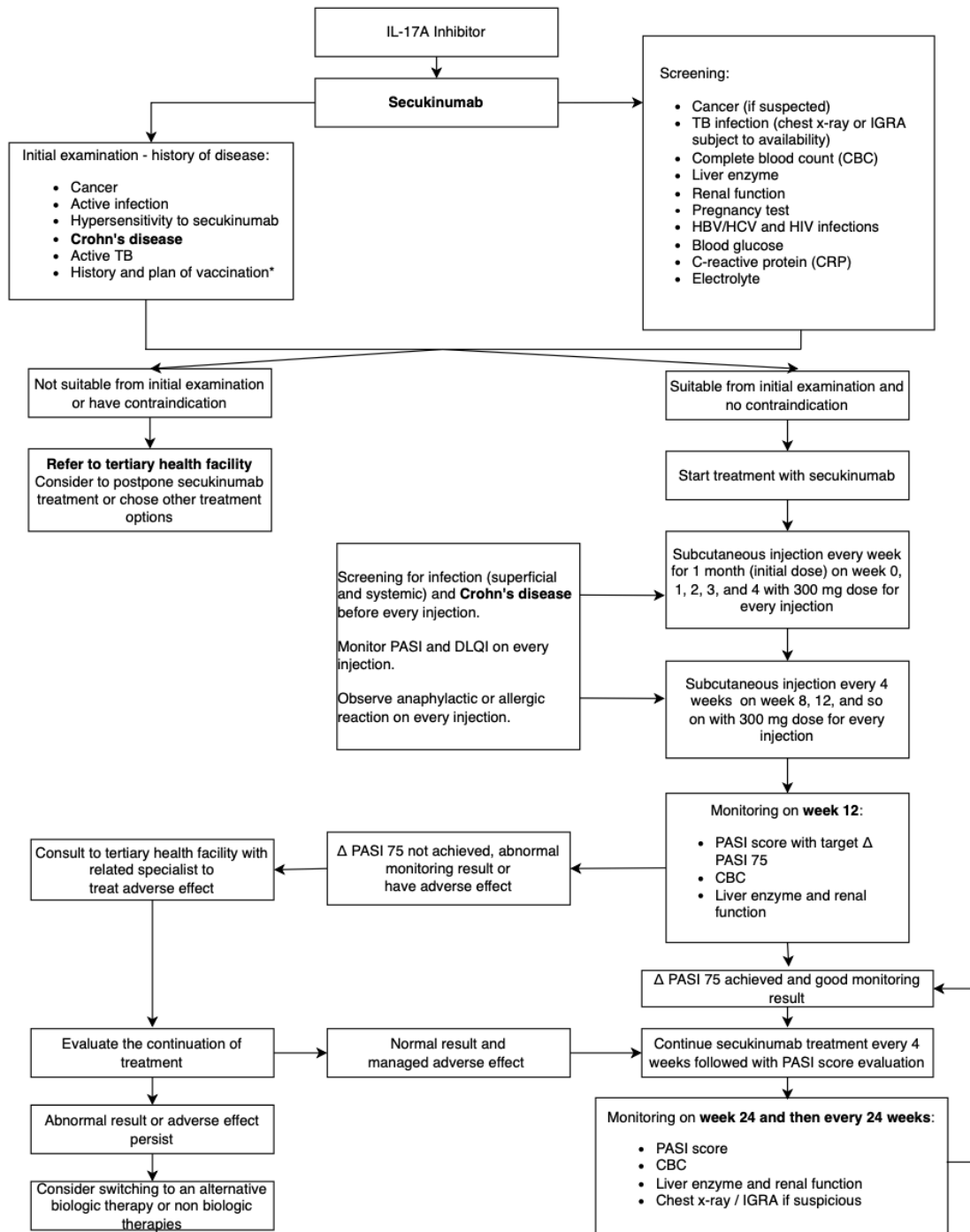
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Figure 4. Cyclosporine A algorithm (A,1) ^{1,3,7-14}



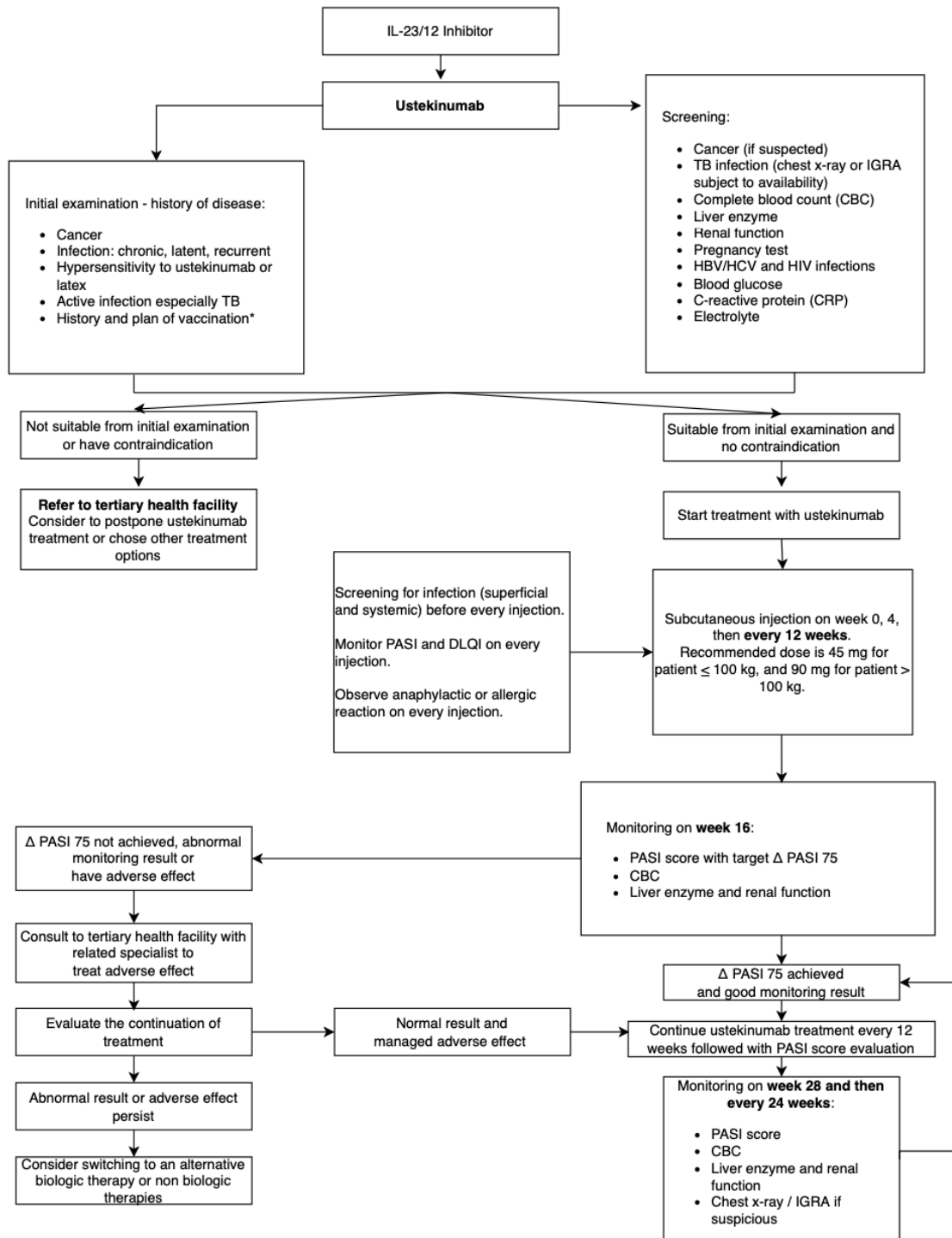
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 5. Secukinumab algorithm (A,1)^{1,3,5,7,8,10-18}



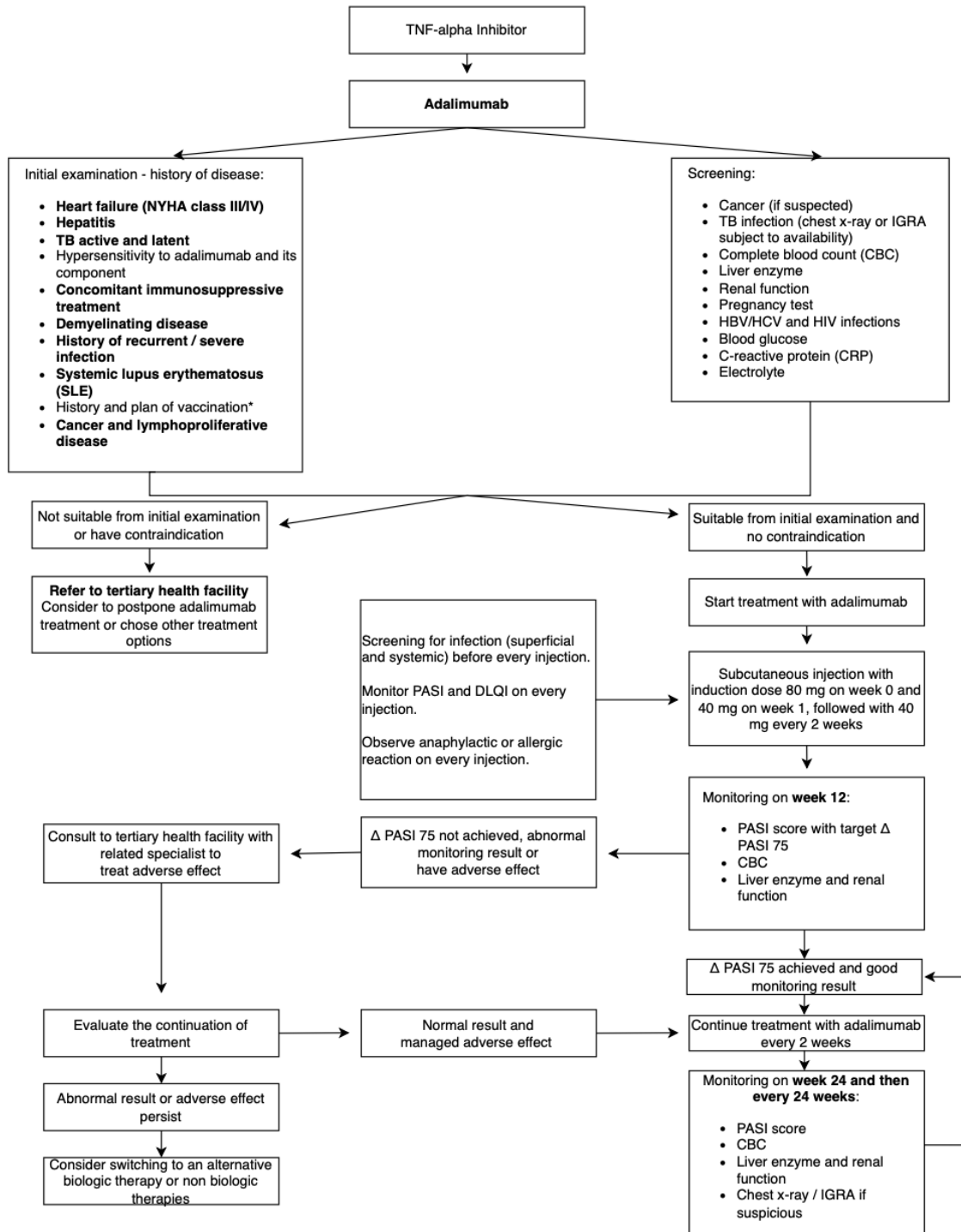
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 6. Ustekinumab algorithm (A,1) ^{1,3,7-15,19,20}



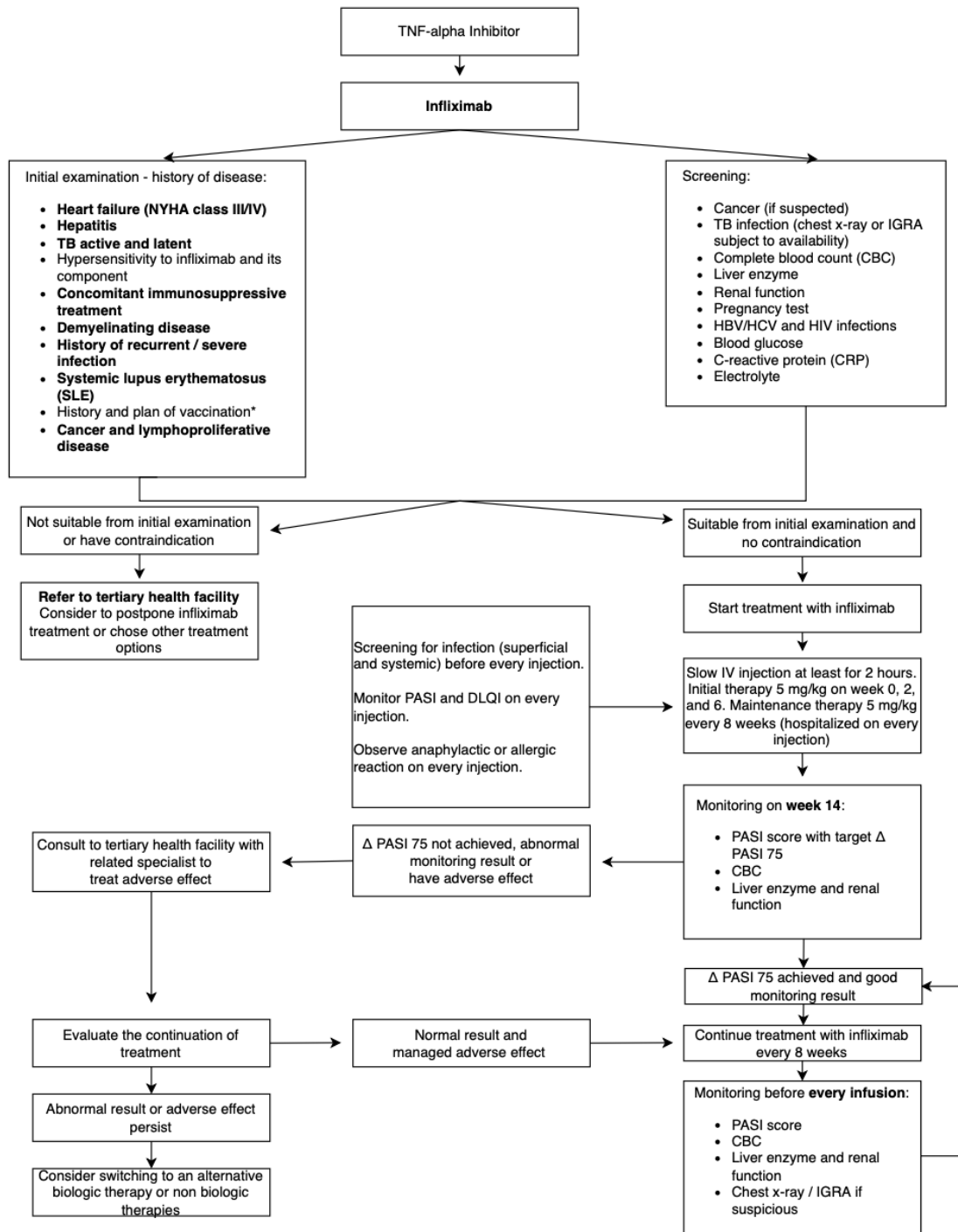
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 7. Adalimumab algorithm (A,1) 1,3,7-15,21,22



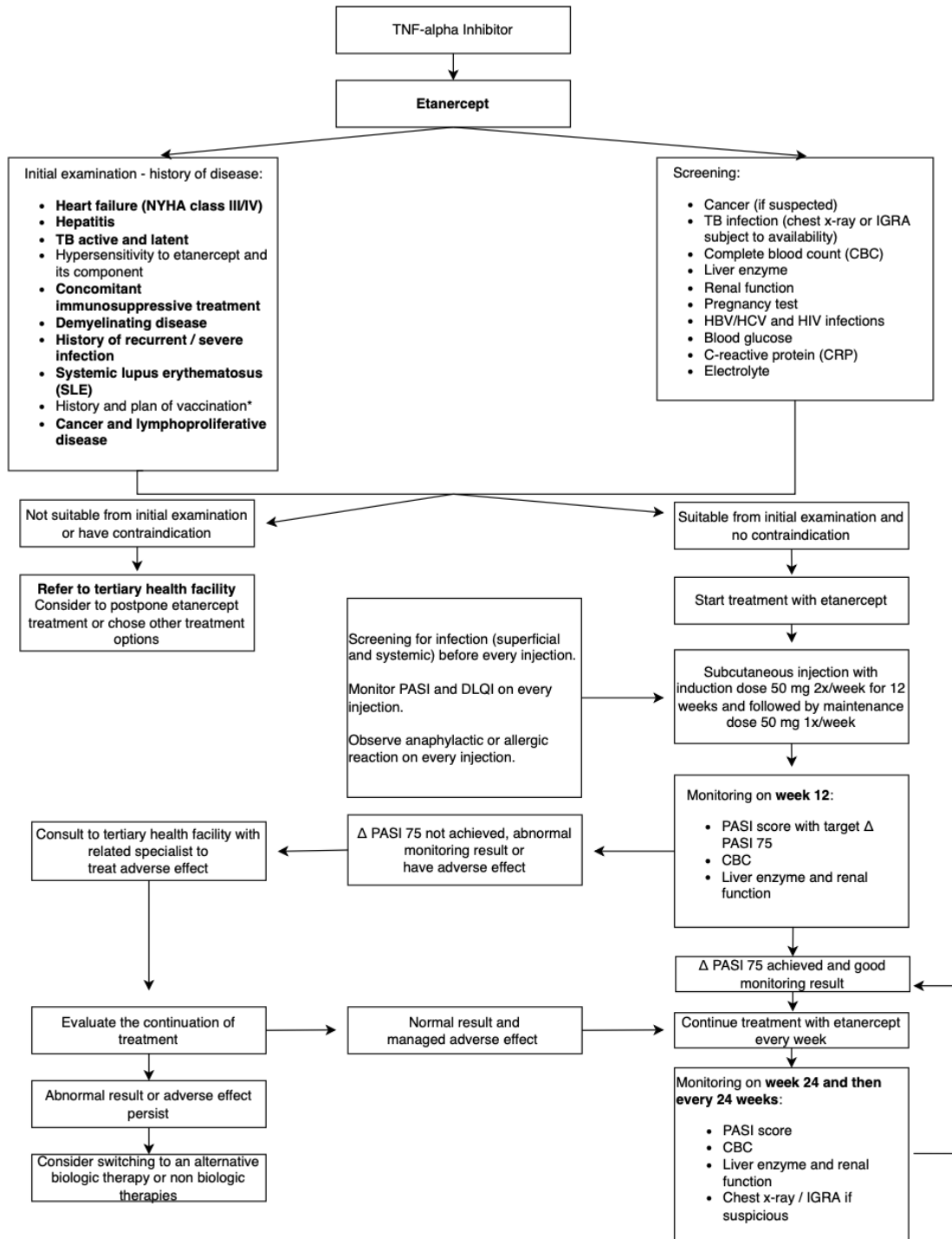
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 8. Infiximab algorithm (A,1) ^{1,3,7-15,22,24}



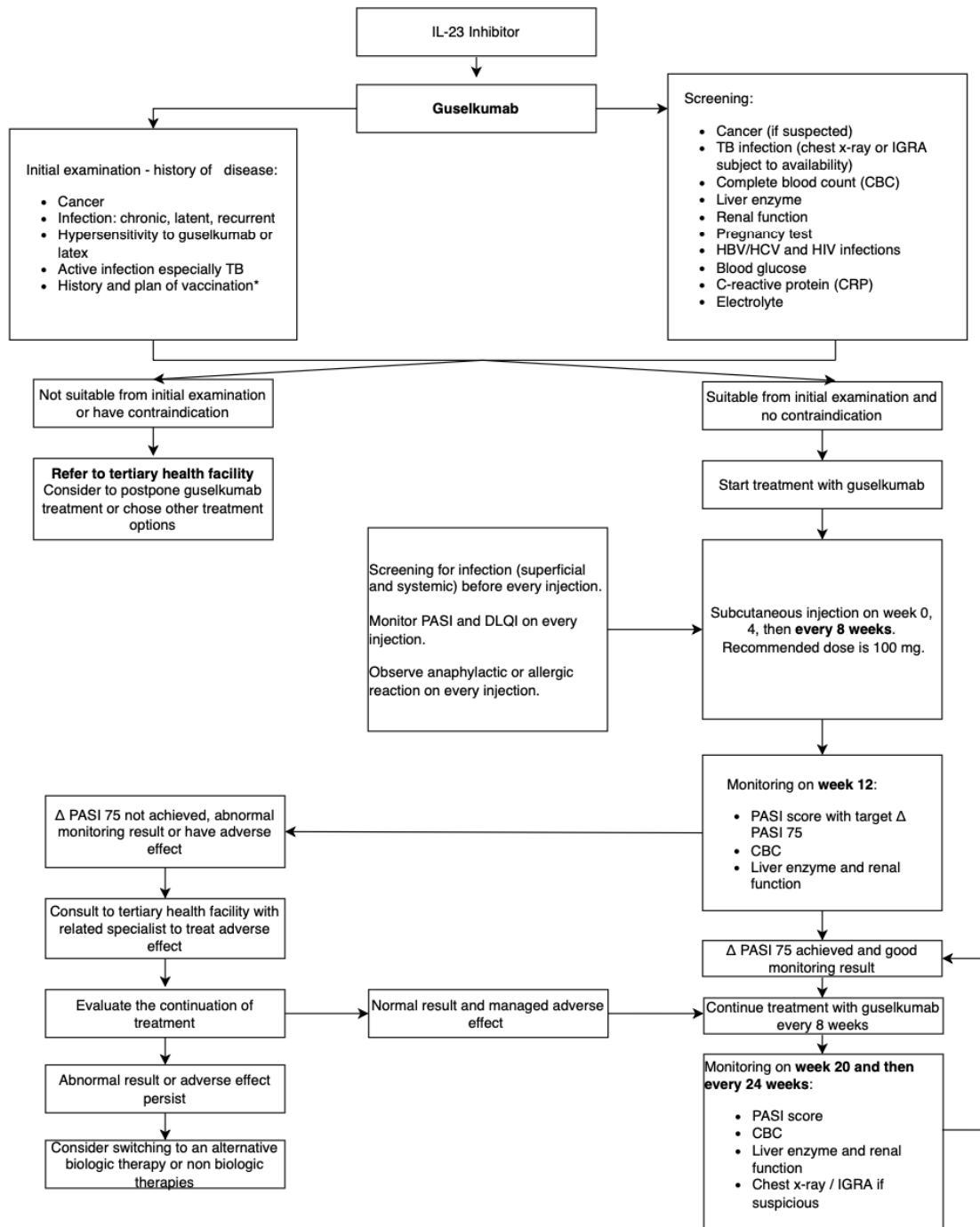
Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 9. Etanercept algorithm (A,1) ^{1,3,7-15,22,25,26}



Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Figure 10. Guselkumab algorithm (A,1) ^{1,3,7-14,21,27-29}



Adapted from *Alur Tata Laksana Psoriasis Vulgaris (Tipe Plak) di Indonesia*¹¹ with modification

Biologic Agent Administration and Vaccination⁴

Inactive vaccines can be given together with all biologic agents.³⁰ For live vaccines, it is recommended to consult with an internist specialized in tropical infectious diseases or allergy immunology. Cessation of biologic agents is recommended before the administration of a live vaccine. Some experts recommend the cessation of treatment with biologic agents before vaccination and postponing the initiation of treatment with biologic agent after vaccination for each 2-3 times the biologic agent's half-life. Other experts advised the cessation of biologic agents four weeks before, and after (or longer, depending on the drug's half-life presented in Table 3.) and until 1-2 weeks after vaccination.^{3,31}

Psoriasis patients who are expected to receive mRNA-based, viral vector, or inactivated COVID-19 vaccines are advised to continue with systemic conventional drug therapy or biologic drugs for psoriasis treatment.^{32,33} If feasible, it is recommended to plan vaccination in the middle of the interval between two-time points of the drug administration.³⁴ Psoriasis patients treated with methotrexate or cyclosporine, however, are advised to temporarily discontinue treatment for five times as long as the half-lives of the drug (about 3-4 days for methotrexate and 5 days for cyclosporine) before vaccination.^{33,34} No conclusive data is available to evaluate the potential effect of systemic immunomodulating or immunosuppressive treatments on COVID-19 vaccination response. The decision should be tailored on a case-by-case basis with shared decision-making between the clinician and patient.³⁴

Discussion

Our guidelines recommend that biologic and non-biologic systemic agents be considered for adult patients diagnosed with moderate to severe plaque psoriasis (Figure 2).

Methotrexate

We recommend that if the patient meets one of the criteria to initiate a systemic treatment, methotrexate (MTX) should be considered the preferred therapeutic option. Patients with moderate to severe psoriasis must be treated by dermatovenerologists. Exceptions to this recommendation include:⁸

- Patients contraindicated for methotrexate.
- Expectant or breastfeeding mothers or patients of either sex who plan to have children in the

near future; we recommend using cyclosporin A instead of methotrexate for these populations.

- Patients with the need for short-term disease control should be considered for cyclosporine instead of methotrexate.

In terms of methotrexate efficacy, 45.2% of patients achieve PASI 75 at 12 or 16 weeks.³⁶ Methotrexate is an inhibitor of folate biosynthesis and therefore impairs DNA replication. This drug was initially used to treat psoriasis due to its cytostatic properties, but its effects on T-cell gene expression patterns have been widely recognized; some of which are related to folate deficiency. Thus, folate supplementation is advisable for patients taking methotrexate to reduce the side effect of MTX. (Figure 3).^{5,11}

The main adverse effects of methotrexate are fatigue, nausea, vomiting, moderate hair loss, elevated transaminases, bone marrow suppression, gastrointestinal and mucosal ulcerations, infections, liver fibrosis, and interstitial pneumonia.^{3,5}

Cyclosporine

Cyclosporine, also known as cyclosporine A (CsA), is a calcineurin inhibitor widely used as an immunomodulator in various conditions, including psoriasis. Cyclosporine inhibits T-cell activation by several mechanisms, including disruption of T-cell receptor signaling, which is the most important and best-understood mechanism in its anti-inflammatory activity.^{5,9}

In terms of efficacy, higher doses of CsA of 5 mg/kg is associated with PASI of 75 in 50-97% of patients, while lower doses of 2.5 mg/kg yielded PASI 75 in 28-85% of patients.³⁷ Contraindications of CsA include hypersensitivity, severe renal dysfunction, uncontrolled hypertension, and malignancy. Therefore, patients with psoriasis receiving CsA should not undergo phototherapy because of the increased risk of cutaneous malignancy.^{9,11}

The main adverse effects of CsA are renal impairment, arterial hypertension, headache, nausea, vomiting, diarrhea, liver dysfunction, gingival hyperplasia, paraesthesia, muscle pain, tremors, hypertrichosis, increased blood lipids, hyperkalemia, and neurotoxicity.^{8,9,11} The period of CsA administration should not exceed 12 months due to its nephrotoxicity for long-term usage.^{9,11,12,13,24} (Figure 4)

Biologic Agents

Due to their potential side effects, screening before biologic agents administration must be done.

History taking and physical examination ruling out alcoholism, gastritis, obesity, infection and other frequently consumed drugs must be conducted. The screening also includes a chest X-ray examination, complete blood count, liver function, renal function, urinalysis, and pregnancy tests.^{3,8,11,12} Biologic agents for adult plaque psoriasis patients must be administered by dermatovenerologists.

Psoriasis patients do not usually require hospitalization, except in cases of severe plaque psoriasis, generalized pustular psoriasis, erythrodermic psoriasis, or psoriasis with other complication.¹

In 2019, secukinumab was registered in the national drug formulation supported by National Health Insurance (JKN) program held by Healthcare and Social Security Agency (BPJS). This inclusion enables physicians to prescribe secukinumab as it is the only biologic agent for psoriasis covered by JKN insurance in Indonesia.

In addition, there has been an additional biologic agent approved by the Indonesian National Agency of Drug and Food Control, guselkumab (A,1), in 2019. Previously, only five biologic agents were available in Indonesia, namely etanercept (Strength of recommendation A, level of evidence 1), ustekinumab (A,1) adalimumab (A,1), infliximab (A,1), and secukinumab (A,1).³

Biologic agents are not considered as the first-line therapy for psoriasis in Indonesia but indicated for moderate to severe psoriasis that has a minimum of one of this criteria:^{3,8,11}

- Adult patients with severe psoriasis who do not respond to at least two standard systemic treatments such as methotrexate, cyclosporine, or phototherapy.
- Contraindicated or intolerant to conventional systemic treatment.

Biologic agents are strongly contraindicated during pregnancy, lactation, age < 18-year old, systemic infections, especially tuberculosis (TB), hepatitis, HIV, malignancy, or neurological defects.^{1,8}

Secukinumab (Figure 5)

Secukinumab is a human immunoglobulin G1-kappa monoclonal antibody that directly inhibits interleukin (IL)-17A. Secukinumab has been shown to have favorable efficacy in the treatment of moderate to severe psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Secukinumab has a great safety profile over long-

term treatment in patients with PsO, PsA, and AS. Reports of secukinumab's safety profile are consistent with previous reports in patients with PsO, PsA, and AS, supporting its long-term use in these chronic conditions.¹⁵

In two-phase III RCTs, ERASURE and FIXTURE, the percentage of patients achieving PASI 75 on week 12 was higher with each secukinumab dose compared with placebo or etanercept: in the ERASURE study, the rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo ($P < 0.001$). The percentages of patients achieving PASI 90 with secukinumab, 300 mg, versus placebo in the ERASURE and FIXTURE studies were 59.2% versus 1.2% and 54.2% versus 1.5%, respectively.^{3,17}

Ustekinumab (Figure 6)

Ustekinumab is a fully human monoclonal antibody that binds to the shared p40 subunit of interleukin 12 (IL-12) and IL-23. Ustekinumab normalizes IL-12- and IL-23-mediated cellular activation events by preventing human IL-12 and IL-23 interaction with their cell surface receptors.^{19,20} Phase II and III trials demonstrated statistically significant improvement of psoriasis and safety of ustekinumab compared with placebo.^{19,20} A PASI 75 was achieved in 67% to 81% of patients with prolonged response to treatment.¹⁹

TNF- α inhibitors

Adalimumab, infliximab, and etanercept are TNF- α inhibitors that share a common mechanism of action that leads to safety concerns such as infections (sepsis, tuberculosis, and viral infections), autoimmune conditions (lupus and demyelinating disorders), and lymphoma. Their causality was difficult to establish in specific patients who developed these conditions during treatment with TNF- α inhibitors.^{21,23-26}

Adalimumab (Figure 7) is a human anti-TNF- α monoclonal antibody. It binds to soluble and membrane-bound TNF- α , inhibiting its interaction with TNF receptors.³ Adalimumab offers effective control of plaque psoriasis. Its clinical effectiveness marked by PASI 75 or higher was maintained for at least one year with continuous therapy. Compared with methotrexate and placebo, adalimumab has been proven to have a higher proportion of patients

achieving PASI 75, 90, and 100 and lower adverse effects.⁵

Infliximab (Figure 8) is a chimeric monoclonal antibody of a mouse variable region and human IgG1, a constant region. Infliximab binds to both soluble and transmembrane TNF- α molecules, neutralizing the effects of TNF- α .³ Infliximab offers rapid and thorough suppression of psoriasis. Nearly half the infliximab-treated patients experienced a decline of at least 90% in PASI score within 10 weeks.^{12,23}

Etanercept (Figure 9) is a modified human tumor necrosis factor- α (TNF- α) receptor protein fused with the Fc portion of IgG1 attached to soluble and membrane-bound TNF- α and tumor necrosis factor- β .³ Etanercept is initiated at a dosage of 50 mg twice a week, reduced to 50 mg/week after 12 weeks of administration. This dosing is sufficient to achieve PASI 75 after 24 weeks in more than half of the patients. However, clearance is observed in patients receiving a constant dosage of 50 mg twice a week. For patients with inadequate responses at 24 weeks, the physician should consider maintaining a constant dosage at 50 mg twice a week rather than stepping down the dose.^{12,24-26}

Guselkumab (Figure 10)

Guselkumab is a fully human IgG1 λ monoclonal antibody that blocks the p19 subunit of IL-23.^{3,27-29} The safety profile for guselkumab remains favorable through 100 weeks of treatment in

patients with moderate-to-severe psoriasis.³ In VOYAGE 2, a phase III RCT, guselkumab was compared with adalimumab and placebo in treating moderate to severe psoriasis. At week 16, a higher percentage of patients receiving guselkumab achieved PASI 90 (70.0% vs 46.8% vs 2.4%) than the groups receiving adalimumab and placebo, respectively.²⁹

Conclusion

The need to treat psoriasis patients must be tailored individually according to patients' indication, comfort, drug safety, and drug availability. The emergence of novel medications with unique mechanisms of action affords significant opportunities for better disease control with minimum toxicity. Recent advances in the treatment of psoriasis have led to newer approaches, including biological agents, that should be integrated into the national consensus of treatment management. Active monitoring and engagement with the patients ensure that the chosen treatment is taken appropriately. Currently, secukinumab is the only biologic agent covered by Indonesian government insurance, but each hospital may have its own regulation in providing the agent.

Acknowledgment

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