COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: An Australian/New Zealand consensus statement

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ABSTRACT

Patients on immunomodulators, including biologic agents and small molecular inhibitors, for cutaneous disease, represent a potentially vulnerable population during the COVID-19 pandemic. There is currently insufficient evidence to determine whether patients on systemic immunomodulators are at increased risk of developing COVID-19 disease or more likely to have severe disease. As such, clinicians need to assess the benefit-to-risk ratio on a case-by-case basis. In patients with suspected or confirmed COVID-19 disease, all immunomodulators used for skin diseases should be immediately withheld, with the possible exception of systemic corticosteroid therapy, which needs to be weaned. In patients who develop symptoms or signs of an upper respiratory tract infection, but COVID-19 is not yet confirmed, consider dose reduction or temporarily cessation for 1–2 weeks. In otherwise well patients, immunomodulators and biologics should be continued. In all patients, and their immediate close contacts, the importance of preventative measures to minimise human-to-human transmission cannot be over emphasised.

Key words: biologic agents, biologics, ciclosporin, COVID-19, dermatology, immunomodulators, Janus Kinase Inhibitors, methotrexate, systemic steroids.

INTRODUCTION

The emergence of the 2019 novel coronavirus SARS-CoV-2, the cause of the COVID-19 pandemic, is the pre-eminent public health issue of this decade. There has been significant global concern due to the widespread and uncertain modes of transmission, and severe disease in a significant proportion. Patients on immunomodulators, including biologic agents and small molecular inhibitors, for cutaneous disease, represent a potentially vulnerable population who require specialised care and advice. Experience and research evidence on COVID-19 is limited; however, we aim to provide guidance for dermatologists and other clinicians in managing and counselling patients who are on immunomodulators.

METHOD

We reviewed the medical literature on COVID-19, and evidence from other human coronavirus and influenza illnesses in patients who are immunosuppressed or on immunomodulator therapy. In addition, expert opinion and clinical experience was shared and debated, and a consensus statement was formulated.
BACKGROUND

SARS-CoV-2 Virology

COVID-19 is the disease caused by an enveloped single-strand RNA virus from the coronavirididae family – SARS-CoV-2. Coronaviruses are so-named due to characteristic ‘crown-like’ projections visible on electron microscopy. Coronaviruses are subdivided into four genera (alpha, beta, gamma and delta) and typically infect birds and mammals. Seven species in the alpha- and beta-coronavirus genera are known to cause human disease from animal-to-human spillover. Other notable disease outbreaks have been caused by coronaviridae including SARS-CoV in 2002–2003 and MERS-CoV in 2012–ongoing.1

Understanding of transmission of SARS-CoV-2 remains incomplete, although it appears to share similar transmission characteristics as SARS-CoV-1.2 Human-to-human transmission is thought to occur predominantly via droplets; transmission via fomites is especially relevant as the virus has been shown to be viable for up to 48–72 h on plastic and steel surfaces.2 Many health services are also assuming airborne precautions, particularly for aerosolised procedures, due to the uncertainty and rapid spread. Indeed, SARS-CoV-2 remained viable in aerosols for around 3 h.2 Detection of the virus in stool samples of COVID-19 patients may suggest potential faecal–oral transmission or asymptomatic shedding in faeces.3 It may also persist on human hair. Transmission from asymptomatic or minimally symptomatic hosts has also been reported, raising the possibility of infectivity during the incubation period.4,5

COVID-19 disease characteristics

The median incubation period for COVID-19 is around 4 to 5 days, but can extend to 1 month.6,7 Severity of the disease peaks around day 7–10, whilst viral shedding usually persists for 3–4 weeks. In most cases, the clinical signs and symptoms are indistinguishable from upper respiratory tract infections. Most commonly reported symptoms in hospitalised cases include the following:6,7,8

- Fever (in almost all)
- Cough (often dry)
- Sputum production
- Coryza
- Myalgia
- Fatigue
- Diarrhoea

Severe disease occurs in around 5–15% of patients and is primarily due to the development of pneumonia/pneumonitis and respiratory failure.5,9 Cardiovascular disease, chronic pulmonary disease, hypertension, diabetes and other chronic medical comorbidities were common in severe, hospitalised cases8 and may be predictors of poor outcome. Smoking may also be a risk factor. Mortality estimates remain imprecise; however, recent case-fatality rates around 2–5% were reported in China.9 Older age is the most important predictor for mortality, with a 15% fatality ratio in patients over the age of 80 in Chinese cohorts.9 Children seem to be at much lower risk of severe disease (especially over the age of 5),10 but may be a significant vector for infection.

Coronavirus in the immunocompromised patient

From previous coronavirus outbreaks, immunosuppression is thought to increase susceptibility and cause more severe infection.11,12 although this is usually in the context of disease driven immunosuppression (e.g. severe inflammatory bowel disease and cancer). Case reports also describe atypical presentations of coronavirus infections in immunocompromised hosts, including prolonged incubation periods, persistent asymptomatic viral shedding, diarrhoea, weight loss and encephalitis as primary manifestations.13,14,15,16

Initial Chinese observational studies on COVID-19 did not report a high rate of immunocompromised patients in severe hospitalised cases; however, this is likely underestimated due to a difference in demography compared to Western populations. Overall, there is currently insufficient evidence to suggest that COVID-19 infection is aggravated by immunomodulators used in skin disease; however, all COVID-19 infections should be considered serious and a precautionary approach is necessary.

Infection risk of immunomodulator and biologic therapies

A range of immunomodulators, including conventional immunomodulators, biologics and newer small-molecule inhibitors, are used in autoimmune and immune-mediated skin diseases. Most conventional immunomodulators are associated with an increased risk of infection. The risk is usually dose-dependent, varies with each agent and often relates more to the underlying health condition being treated. Table 1 summarises commonly used non-biologic immunomodulators and their infection risks. Although immunomodulatory in action, retinoids (including acitretin, isotretinoin, alitretinoin), dapsone and phosphodiesterase (PDE)-4 inhibitors are not immunosuppressive.

Recently, biologic agents such as monoclonal antibodies and small-molecule agents such as Janus kinase (JAK) and PDE-4 inhibitors have provided a novel approach in the treatment of various skin diseases. By targeting single molecules or proteins that are critical in the disease pathogenesis, immunomodulation is thought to be more selective. Table 2 summarises the short-term rates of upper respiratory tract infection and serious infection in pivotal phase III clinical trials for biologics and small-molecule agents.

Overall, some biologics and small-molecule inhibitors have a small increase in upper respiratory tract infections or nasopharyngitis in clinical trials; however, infections are usually mild or self-limiting and serious infection rates are very low. There is no high-quality evidence to suggest that biologics used in otherwise healthy dermatology patients is associated with an increased rate of severe
infection or more severe influenza illnesses. On the other hand, patients with severe skin disorders (e.g. severe psoriasis) are inherently at increased risk of developing pneumonias, of any cause. Furthermore, discontinuation of biologic therapy may result in a loss of treatment response when rechallenged and/or development of drug antibodies.

If cessation of a biologic is being considered due to the pandemic, patients should be unambiguously counselled on the aforementioned risks. Please consider registering your patient with the Australasian Psoriasis Registry (or equivalent international registry) so experiences can be shared. Nonetheless, transmission prevention measures should be emphasised in all patients and their immediate contacts, as this is likely the most effective measure to prevent SARS-CoV-2 infection.

### Risk assessment and management for patients on immunomodulators

- There is currently insufficient evidence to determine whether dermatology patients on systemic immunomodulators are at increased risk of developing COVID-19 infection or more likely to have severe disease; as such clinicians need to assess the benefit-to-risk ratio on a case-by-case basis.

- Patient factors that may indicate a higher risk of severe COVID-19 disease include the following:
  - a. Age over 60.
  - b. Uncontrolled or multiple chronic comorbidities including, but not limited to cardiovascular or chronic pulmonary disease, chronic kidney disease, diabetes, hypertension and some malignancies.
  - c. High doses or multiple immunomodulators.
  - d. History of severe or recurrent respiratory tract infections.

  - For most patients who are low-risk, immunomodulators should be continued.
  - Dose reductions (see Table 5 on possible lower dosages) or drug cessation may be considered in those who are identified as high risk; however, care should be taken with dose reduction of corticosteroid therapy.
  - Dose reduction or cessation of immunomodulators and biologics is not necessary in most children.

### Corticosteroid therapy during the COVID-19 pandemic

- Corticosteroids are significantly immunosuppressive at dosages above 20 mg prednisolone equivalent; long-term use of such dosages during the pandemic should be avoided.
- Use of prednisolone at 15 mg or more for 5 weeks is also associated with adrenal axis suppression.
- We recommend against sudden cessation or significant dose reductions due to risks of adrenal insufficiency. Indeed, corticosteroid therapy may need to be increased in times of physiological stress including COVID-19, acute respiratory distress syndrome and other serious infection.
- If reduction of corticosteroid therapy is indicated to mitigate infection risk during the pandemic, a graduated reduction is advised, aiming for a dose of ≤10 mg of prednisolone or equivalent.

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Immunomodulators during COVID-19 pandemic

Table 2  Rate of respiratory infections for biologics and small-molecule agents at primary endpoint analysis during pivotal phase III dermatology trials

| Class and main indication in dermatology | Agent | URTI rate (treatment:placebo) | Nasopharyngitis rate (treatment:placebo) | Serious infection rate (treatment:placebo) |
|----------------------------------------|-------|-------------------------------|------------------------------------------|------------------------------------------|
| TNF-alpha inhibitors (psoriasis)       | Adalimumab (n = 1212) | 7.2% vs. 5.5% | 5.5% vs. 6.5% | 1.8% vs. 1.8% |
|                                        | Inflixiab (n = 578) | 15% vs. 16% | NA | NA |
|                                        | Etanercept (n = 611) | 15% (high dose) vs. 15% (low dose) vs. 15% | 10.2% (high dose) vs. 8.2% (low dose) vs. 8.6% | 1 case in placebo only |
| IL-12/23 inhibitor (psoriasis)         | Ustekinumab (n = 766) | 7.1% (high dose) vs. 6.3% (low dose) vs. 5.3% | 10.7% (high dose) vs. 15.8% (low dose) vs. 11.1% | 0.0% (high dose) vs. 0.8% (low dose) vs. 0.4% |
| IL-17 inhibitors (psoriasis)          | Secukinumab (n = 758; 2 trials) | 2.1% (high dose) vs. 3.1% (low dose) vs. 2.2% | 7.1% (high dose) vs. 6.3% (low dose) vs. 5.7% | 0.0% (high dose) vs. 0.7% (low dose) vs. 0.4% |
|                                        | Ikemizumab (n = 1296; 2 trials) | 4.4% (high dose) vs. 5.9% (low dose) | 9.5% (high dose) vs. 9.9% (low dose) | 0.4% (high dose) vs. 0.7% (low dose) |
|                                        | Brodalumab (n = 1776; 2 trials) | 5.4% (high dose) vs. 4.9% (low dose) vs. 7.4% | 7.4% (high dose) vs. 7.4% (low dose) vs. 4.7% | 1% (high dose) vs. 2.1% (low dose) vs. 2.6% |
| IL-25 inhibitors (psoriasis)           | Guselkumab (n = 992) | 5.1% vs. 2.8% | 7.1% vs. 6.5% | 0.2% vs. 0.4% |
|                                        | Risankizumab (n = 997; 2 trials) | 5% vs. 4% | NA | 2.2% vs. 2% |
| IL-4 and IL-15 inhibitors (atopic dermatitis) | Tildrakizumab (n = 1862; 2 trials) | 2.4% (high dose) vs. 1.6% (low dose) vs. 2.9% | 8.8% (high dose) vs. 10.6% (low dose) vs. 6.5% | 0.5% (high dose) vs. 0.2% (low dose) |
|                                        | Dupilumab (n = 1579; 2 trials) | 5% (high dose) vs. 2.6% (low dose) vs. 2.3% | 11.5% (high dose) vs. 9.6% (low dose) vs. 7.7% | 0.9% (high dose) vs. 1.1% (low dose) vs. 2.9% |
| IgE inhibitor (chronic spontaneous urticaria) | Omalizumab (n = 523) | 1.5% (high dose) vs. 1.3% (low dose) vs. 1.3% | 12.7% (high dose) vs. 17.1% (low dose) vs. 16.5% | 0% (high dose) vs. 1.3% (low dose) vs. 2.5% |
| Janus kinase inhibitors (atopic dermatitis) | Baricitinib (n = 1259; 2 trials) | 5.2% (high dose) vs. 2.8% (low dose) vs. 2.2% | 8.9% (high dose) vs. 13.9% (low dose) vs. 11.4% | 1.2% (high dose) vs. 4.0% (low dose) vs. 5.0% |
| PDE-4 inhibitors (psoriasis)           | Apremilast (n = 844) | 10.2% vs. 7.4% | 7.5% vs. 8.2% | Nil in placebo-controlled period |
| Anti B-cell (anti-CD20)                | Rituximab (n = 520; rheumatoid arthritis trial) | 7.8% vs. 6.7% | 7.5% vs. 5.7% | 2.3% vs. 1.4% |

Imbalances of greater than twofold between treatment and placebo have been bolded. NA, not available. URTI, upper respiratory tract infection.

Rates of serious infection in patients with rheumatoid arthritis treated with rituximab appear to be dose related; serious infections that have been reported include HBV reactivation, Pneumocystis carinii and JC virus.

Patients on immunomodulators with an upper respiratory tract infection (URTI)

- In patients who develop symptoms or signs of an upper respiratory tract infection (but COVID-19 is not suspected), consider dose reduction or temporarily cessation for 1-2 weeks/until resolution.
- Screen for non-COVID-19 respiratory pathogens, for example, influenza/RSV that can occur independently or as a co-infection with SARS-CoV-2.
- Patients should be referred for COVID-19 testing if they meet local testing criteria, and isolation until confirmation of COVID-19 testing results.

Patients on immunomodulators with suspected or confirmed COVID-19 infection

- In patients with suspected or confirmed COVID-19 infection, all immunomodulators used for skin diseases should be immediately withheld, with the possible exception of corticosteroid therapy (as outlined above).
- For patients on a biologic agent, withhold or postpone the next dose if it falls within 31 days of infection onset (based on potential length of viral shedding).
- Only recommence biologic therapy upon resolution of illness and/or confirmation of negative PCR testing indicating no viral shedding.

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Table 5 Possible lower dosages of immunomodulators

| Agent                  | Elimination half-life | Possible lower dose |
|------------------------|-----------------------|---------------------|
| Ciclosporin            | 5 h                   | Reduce to ≤0.5 mg/kg/day |
| Cyclosporin            | 5–18 h                | Reduce to ≤1 mg/kg/day   |
| Methotrexate           | 25–50 h               | Reduce to ≤10 mg/week    |
| Mycophenolate mofetil  | 8–16 h                | Reduce to ≤1 g/day (mofetil) |
| Systemic corticosteroids | Prednisol(n) 3–4 h | Reduce to 10 mg/day prednisone equivalent in a graduated manner. |
| Retinoids              |                      | No dose adjustment required. |
| Biologics              | Variable              | Dose reduction often not possible but consider extending the time between dosages. Temporary discontinuation should be evaluated on a case-by-case basis. |

• Conventional immunomodulators should be withheld for 51 days from infection onset and recommended after complete resolution of illness and/or confirmation of negative PCR testing indicating no viral shedding.
• Clinicians should maintain a high index suspicion for severe infection if discontinuation of immunomodulators is not possible or limited recovery despite discontinuation.

Organ Transplant/Bone marrow transplant patients

• Solid organ transplant/bone marrow patients: it is essential that the patient and their immediate close contacts strictly adhere to isolation and other preventative measures.
• Immunosuppressive treatments (e.g. prednisone, ciclosporin, tacrolimus, azathioprine and mycophenolate) should not be altered without obtaining specific advice from the transplant physician/surgeon.

Initiation of immunomodulators during the COVID-19 pandemic

• Until further evidence is available, we advise caution commencing new immunomodulators until the pandemic is controlled.
• Initiation of immunomodulators in patients who suffer from severe skin disease should be made in conjunction with the patient; an informed decision needs to be made with risks and benefits clearly outlined.
• Caution should be exercised when initiating immunomodulatory agents associated with a definite increased risk of severe infection especially TNF-alpha inhibitors, rituximab and some non-biologic immunomodulators. Reduced doses may be considered.

Preventative measures during COVID-19 pandemic

In all patients, we emphasise the importance of preventative measures to minimise human-to-human transmission, including but not limited to:19

• Regular washing of hands with soap and water; especially prior to applying creams to the face and body. Delay using emollient hand creams for 10–30 min after washing hands.
• Avoid touching of face, eyes or mouth with unwashed hands.
• Covering mouth and nose whilst coughing or sneezing.
• Avoiding overseas or interstate travel.
• Staying at home unless for medical care or necessary work.
• Avoid sharing of household items such as cutlery and towels.
• Regular cleaning of high-touch everyday objects.
• Wearing a face mask is not necessary if you are well.
• Practice good social-distancing techniques - this includes standing at least a metre and a half from the person standing next to you.
• Stop shaking hands, hongi, kissing or hugging as a greeting.
• Avoiding large gatherings, crowded places, or enclosed spaces (e.g. lifts).
• For cleaning around the house, any usual household detergent should be effective at killing SARS-CoV-2.
• Follow the current advice from your state/federal government regarding non-essential activities.

In addition, we recommend annual influenza vaccination (except live intranasal influenza vaccines) for all and pneumococcal vaccination in appropriate populations. Note that vaccine effectiveness may be diminished by higher dosages of some immunomodulators.

Follow-up of dermatology patients on immunomodulators

In addition to minimising risk, it is important to consider rational use of health-care resources during the COVID-19 pandemic:

• Consider conducting follow-up visits by telemedicine.20
• Consider reducing the frequency of routine monitoring investigations.21
• Re-enforce advice to improve comorbidities, in particular smoking and obesity.
• For omalizumab, after the first injections, consider letting patients self inject at home.

CONCLUSION

This consensus statement draws upon the knowledge and experience of dermatologists specialised in the care of the immunosuppressed patient. More data and studies are required in characterising COVID-19 disease and its
management in patients on immunomodulators. Ultimately, we advocate for a cautious clinical approach in this rapidly evolving global health emergency.

REFERENCES

1. Zhu N, Zhang D, Wang W et al. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020; 382: 727–33.
2. Doremalen N, Bushmaker T, Morris DH et al. Aerosol and Surface Stability of SARS-CoV-2 as compared with SARS-CoV-1. N. Engl. J. Med. 2020; 382: 1564–7.
3. Young BE, Ong SW, Kalimuddin S et al. Characteristics and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in Wuhan, China. From the Coronavirus Disease 2019 (COVID-19) Outbreak in China, 2019. N. Engl. J. Med. 2020; 382: 1564–71.
4. Zhou F, Yu T, Du R et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1123–32.
5. Wang D, Han B, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1123–32.
6. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.
7. Wu Z, McGoogan JM. Characteristics and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA 2020; 323: 1239–42.
8. Dong YY, Mo X, Hu YB et al. Epidemiological characteristics of 2143 paediatric patients with 2019 coronavirus disease in China. Paediatrics 2020; e20200702. https://doi.org/10.1542/peds.2020-0702.
9. Trombetta H, Faggion HZ, Leotte J et al. Human coronavirus and severe acute respiratory infection in Southern Brazil. Pathog. Glob. Health 2016; 110: 115–8.
10. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) – Fact Sheet. World Health Organisation. Published online 11 March 2019. Available from: https://www.who.int/en/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov).
11. Kim SH, Ko JH, Cho SY et al. Atypical presentations of MERS-CoV infection in immunocompromised hosts. J. Infect. Chemother. 2017; 23: 769–75.
12. Guery B, Puissy J, el Mansouf I et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet 2015; 381: 2265–72.
13. Omar A, Patil PD, Hoshi S et al. A 68-year-old lung transplant recipient with shortness of breath, weight loss and abnormal chest CT. Chest 2018; 155: 155–7.
14. Morfopoulou S, Brown J, Qasim W et al. Human coronavirus OC43 associated with Fatal Encephalitis. N. Engl. J. Med. 2016; 375: 497–8.
15. Rademaker M, Agnew K, Anagnostou N et al. Psoriasis and infection. A clinical practice narrative. Australas. J. Dermatol. 2019; 60: 91–8.
16. Jung C, Inder WJ. Management of adrenal insufficiency during the stress of medical illness and surgery. Med. J. Aust. 2008; 188: 409–15.
17. CDC. Preventing the Spread of Coronavirus Disease 2019 in Homes and Residential Communities. Centres for Disease Control and Prevention. Updated 14 February 2020. Available online from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-prevent-spread.html.
18. Taylor M, Abbott L, Miller R et al. Practice guidelines for tele-dermatology in Australia. Australas. J. Dermatol. 2020; 61: 9–22.
19. McLean–Tooke A, Aldridge C, Waugh S et al. Methotrexate, rheumatoid arthritis and infection risk – what is the evidence. Rheumatology 2009; 48: 867–71.
20. Ibrahim A, Ahmed M, Conway R et al. Risk of infection with methotrexate therapy in inflammatory diseases: A systemic review and meta-analysis. J Clin Med. 2018; 7: pii: E15.
21. Lopez-Olivo MA, Siddhanamatha HR, She B et al. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst. Rev. 2014: CD000957.
22. Berth-Jones J, Exton LS, Ladoyanni E et al. British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018. Br. J. Dermatol. 2018; 180: 1512–38.
23. Krupp P, Monka C. Side-effect profile of cyclosporine A in patients treated for psoriasis. Br. J. Dermatol. 1990; 122: 47–56.
24. De Wilde A, Raj VS, Oudshoorn D et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporine A or interferon-alpha treatment. J. Gen. Virol. 2015; 94: 1749–60.
25. Bernatsky S, Hudson M, Sussa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology 2007; 46: 1147–60.
26. Anstey JV, Wakelin S, Reynolds NJ. Guidelines for the prescribing azathioprine in dermatology. Br. J. Dermatol. 2004; 151: 1125–52.
27. Seksik P, Cosnes J, Sokol H et al. Incidence of benign upper respiratory infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. Aliment. Pharmacol. Ther. 2009; 29: 1106–13.
28. Ritter ML, Pirofski L. Mycophenolate Mofetil: effects on cellular immune subsets, infectious complications, and anti-microbial activity. Transpl. Infect. Dis. 2009; 11: 290–7.
29. Doernner T. Hydroxychloroquine in SLE: old drug, new perspectives. Nat. Rev. Rheumatol. 2010; 6: 10–11.
30. Colson P, Rolain J, Lagier C et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; 105952.https://doi.org/10.1016/j.ijantimicag.2020.105952.
31. Menter A, Tyring SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J. Am. Acad. Dermatol. 2008; 58: 106–15.
32. Reich K, Nestle FO, Papp KA et al. Infliximab induction and maintenance therapy for moderate to severe psoriasis: a phase III, multicenter, double-blind trial. Lancet 2005; 366: 1367–74.
33. Papp KA, Tyring S, Lafla M A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy and effect of dose reduction. Br. J. Dermatol. 2005; 152: 1504–12.
34. Leonard CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/25 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1655–74.
35. Langley RG, Elewski BE, Lehrbod M et al. Secukinumab in plaque psoriasis – results of two phase 5 trials. N. Engl. J. Med. 2014; 371: 526–38.
36. Gordon KB, Blauvelt AB, Papp KA et al. Phase 3 trials of Ixekizumab in moderate-to-severe plaque psoriasis. N. Engl. J. Med. 2016; 375: 345–56.
40. Lebwohl M, Strober B, Menter A et al. Phase 3 studies comparing brodalumab with Ustekinumab in Psoriasis. N. Engl. J. Med. 2015; 375: 1518–28.
41. Reich K, Armstrong AW, Foley P et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody compared with adalimumab for the treatment of moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J. Am. Acad. Dermatol. 2017; 76: 418–451.
42. Gordon KB, Strober B, Lebwohl M et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltiMMA-1 and UltiMMA-2): results from two double-blind, randomised placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet 2019; 594: 576–86.
43. Reich K, Papp KA, Tyring SK et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 2017; 590: 276–88.
44. Simpson EL, Bieber T, Guttmann-Yassky E et al. Two phase 3 trials of Dupilumab versus Placebo in atopic dermatitis. N. Engl. J. Med. 2016; 375: 2535–48.
45. Maurer M, Rosen K, Hsieh HJ et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N. Engl. J. Med. 2015; 368: 924–935.
46. Simpson EL, Lacour JP, Spelman I et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br. J. Dermatol. 2020. https://doi.org/10.1111/bjd.18898.
47. Papp KA, Reich K, Leonardi C et al. Apremilast, an oral phosphodiesterase 5 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J. Am. Acad. Dermatol. 2015; 73: 57–49.
48. Cohen SB, Emery P, Greenwald MW et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006; 54: 2793–806.