A RESEARCH REVIEW™
EXPERT FORUM

Immune-Mediated Inflammatory Disease (IMID) Virtual Clinical Education Meeting

Making Education Easy

23rd September 2020, Virtual Meeting

In this review:

Abbreviations used in this review

Anti-CCP = anti-cyclic citrullinated peptide
ATP = adenosine triphosphate
CD = Crohn's disease
DLQI = Dermatology Life Quality Index
GP = general practitioner
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue
HiSCR = Hidradenitis Suppurativa Clinical Response
HiSQoL = Hidradenitis Suppurativa Quality of Life
HS = hidradenitis suppurativa
IBD = inflammatory bowel disease
IL = interleukin
JAK = Janus kinase inhibitor
PHQ-9 = Patient Health Questionnaire 9
PGA = Physician Global Assessment
QoL = quality of life
RA = rheumatoid arthritis
SF-36 = 36-Item Short Form Survey
TNF = tumour necrosis factor
WPAI = Work Productivity and Activity Impairment

This publication is a summary of selected presentations delivered at the AbbVie-sponsored Immune-Mediated Inflammatory Diseases (IMID) Virtual Clinical Education Meeting, held on September 23rd 2020.

HOW TO ACHIEVE THE BEST OUTCOMES FOR HIDRADENITIS SUPPURATIVA PATIENTS WITH HUMIRA® – A PANEL DISCUSSION

– Adjunct Associate Professor Amanda Oakley
– Dr Diana Rubel

Adjunct Associate Professor Amanda Oakley CNZM

Adjunct Associate Professor Amanda Oakley is an experienced dermatologist from Hamilton, New Zealand. She is passionate about dermoscopy, teledermatology and online health education for patients and their doctors, but is happy to talk and write about a wide variety of dermatological topics. Amanda is a specialist dermatologist at Waikato Hospital and an Adjunct Associate Professor at Waikato Clinical Campus, Auckland University School of Medicine. She is the Founder of DermNet NZ, and a diagnosing consultant for MoleMap NZ. She has received various awards for her research and dedication to dermatology including Companion of the New Zealand Order of Merit in 2018 and Kudos Lifetime Achievement Award in 2019, as well as honorary membership of the American Academy of Dermatology, the American Dermatological Society, MelNet, and the Royal New Zealand College of General Practitioners.

Dr Diana Rubel

Dr Diana Rubel is a consultant dermatologist in private practice at Woden Dermatology, Canberra, a Visiting Medical Officer at Canberra Hospital, and Senior Lecturer at The Australian National University. Diana has over 15 years' experience at the Skin and Cancer Foundation, Darlinghurst, Sydney, and has been a Staff Specialist at the Sydney Children's Hospital for 10 years. Her goal is to excel in patient care and service to her patients, her referring doctors, and her staff. She is passionate about consistently delivering high-quality care to all patients, and has developed special interests in skin cancer management, paediatric dermatology, acne, psoriasis, cosmetic dermatology, and clinical trials.

How does hidradenitis suppurativa (HS) normally present?

Associate Professor Oakley explained that the presentation of HS is typical in most patients. The typical patient is a young adult, although HS can present from puberty to old age.[1] The condition is reported to be more common in females than males and can affect any ethnicity, although reports from the US suggest that HS is more prevalent in African Americans than other ethnic groups.[1,2] Over half of patients are obese and greater than 70% are past or current smokers.[1] Other skin conditions, particularly acne, are frequently seen.[1]

The symptoms and signs of HS are fairly simple to recognise and most often comprise chronic painful inflamed lesions in the axillae, groin, submammary folds, perianal region, and, in a few patients, the buttocks, mons pubis, post auricular area, scalp and back.[2] The characteristic feature of HS is of a recurring disease over many years, involving papules, nodules, comedones, pustules, pseudocysts, abscesses, fistulae, sinus tracts, scars, and pleated ridges of skin (**Figure 1**).[2-4] Symptoms are exacerbated by physical activity, sweating, shaving and friction.[2]

Comorbidities are common in patients with HS and many are inflammatory in nature.[2] Comorbidities in HS include cardiovascular disease, metabolic syndrome, obstructive sleep apnoea, diabetes mellitus, hypertension, psoriasis, spondyloarthropathy, and Crohn's disease (CD).[2] In the Netherlands, it has been reported that 17% of patients with CD exhibit symptoms of HS.[5] Not surprisingly, patients with HS report decreased QoL, depression (present in up to 43%), anxiety, embarrassment, substance abuse, unemployment (21-25%), and an increased risk of suicide (2-fold higher than that in psoriasis patients).[2]

Dr Rubel commented that in the majority of cases HS is relatively easy to diagnose and that most GPs should be able to make the diagnosis.

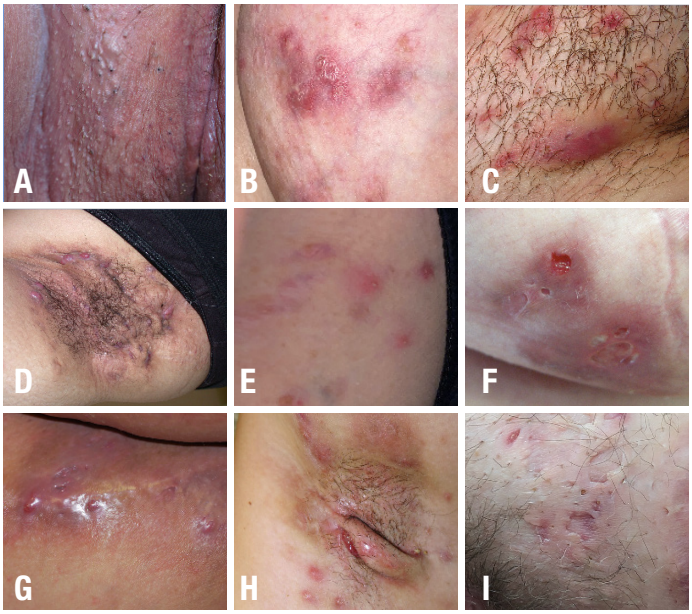


Figure 1. Clinical features of HS. (A) Comedones, (B) Papules, (C) Nodules, (D) Pseudocysts, (E) Pustules, (F) Abscesses, (G) Draining sinuses, (H) Pleated skin, (I) Scars.

What are the treatment goals and what factors are important for patients?

Dr Rubel explained that HS is a very difficult disease to treat and it is also difficult to measure the impact of therapeutic interventions. Treatment goals comprise patient- and physician-orientated goals. Measures of patient-reported outcomes include the Dermatology Life Quality Index (DLQI), pain scores, impact on work scores, and the newly-developed Hidradenitis Suppurativa Quality of Life (HiSQoL) score.[6,7] The HiSQoL, a 17-item instrument, has been developed to capture features such as drainage and odour that are not captured by general QoL tools.[7]

The most commonly used physician-reported severity classification for HS was developed by Hurley and has routinely been used in clinical practice.[2] Dr Rubel explained that while the Hurley score is good for grading the severity of HS, it is limited in that it does not globally address the patients disease, nor response to treatment, and is therefore not ideal for monitoring overall disease progress.[2] She prefers to use the Hidradenitis Suppurativa Clinical Response (HiSCR), a dichotomised clinical tool that measures treatment response.[2] Other physician-oriented tools include the modified Sartorius score and the Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA), but these carry a degree of inter-rater variability.[2]

How can HS be treated?

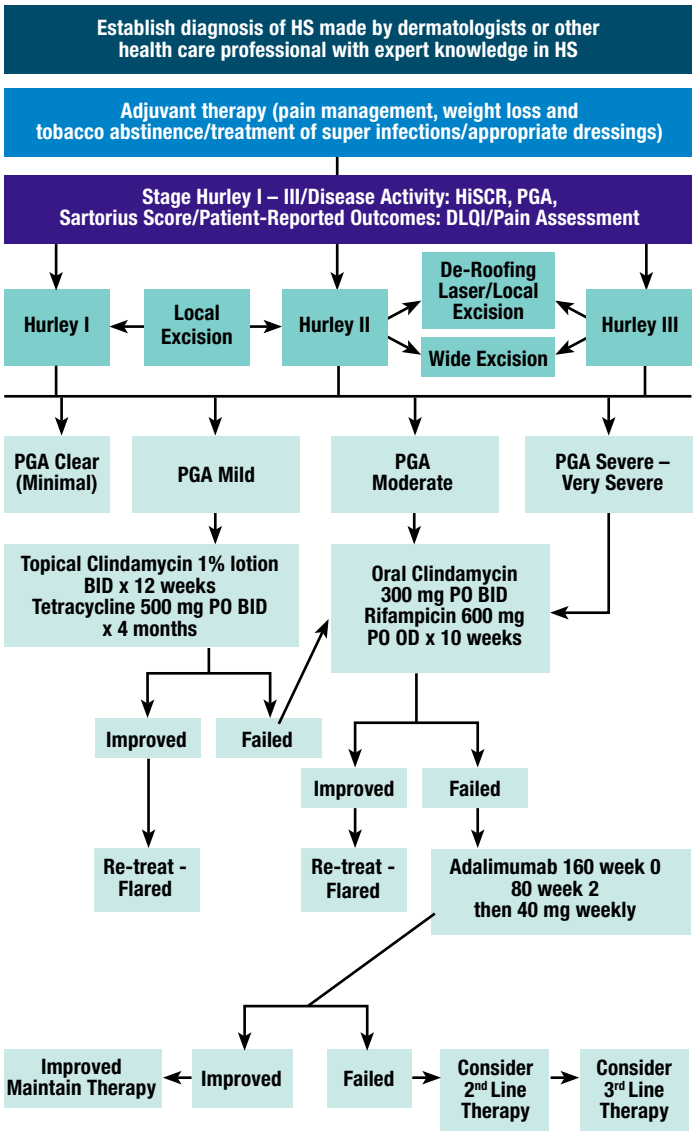
Associate Professor Oakley reiterated that the treatment of HS is very challenging and, due to the paucity of research in this area, the treatments used are often based on limited data and expert opinion. She explained that the only biologic that is approved for the treatment of HS is adalimumab, which is registered in a number of countries. She emphasised that patients should be informed that while they can be treated for symptoms, HS is a chronic disease with no cure. Patients must be educated about the factors that aggravate HS and be encouraged to lose weight if necessary and to quit smoking. A weight loss of 15% has been associated with less severe disease and weight loss surgery has proven beneficial.[8] HS patients who quit smoking have been shown to experience a better response to treatment.[9]

Associate Professor Oakley emphasised that psychological support, pain management and wound care education are all essential elements of treatment in patients with HS. She explained that flare-ups of HS may require a step up of pain management, that abscesses may require incisional treatment and drainage in hospital, that staphylococcal infection may require a short course of antibacterials, and that nodules may benefit from intralesional corticosteroid treatment.

Treatment for chronic moderate-to-severe HS usually begins with an antibiotic and according to Associate Professor Oakley, the most commonly prescribed antibiotic in New Zealand for HS is doxycycline.[9] She explained that response to antibiotic treatment is usually assessed at 12 weeks (by counting the number of red nodules and abscesses), by which time some patients may have experienced disease clearance, while others may require extended antibiotic treatment for a number of months. Patients with persistent moderate-to-severe HS may require treatment with a biologic agent. In New Zealand, the only approved and fully funded biologic for the treatment of HS is adalimumab [Humira®], which is available via special authority and only for applications from a dermatologist.[10] In New Zealand, adalimumab is indicated for the treatment of moderate-to-severe HS in adults and adolescents aged ≥12 years weighing a minimum of 30 kg with an inadequate response to conventional systemic HS therapy.[11]

The efficacy of weekly adalimumab was demonstrated in patients with moderate-to-severe HS in the phase 3 PIONEER 1 and 2 trials, with a pooled analysis showing achievement of HiSCR at week 12 in approximately 50.6% versus 27% of placebo recipients ($p< 0.001$), with this response maintained at 168 weeks, as well as sustained improvements in DLQI scores to week 72.[12]

Dr Rubel agreed that it is very important to treat patients with HS holistically and to reduce comorbidities and the consequences of the disease such as pain and depression. She presented a treatment algorithm for HS (**Figure 2**) and explained that while simpler lesions may be able to be successfully treated surgically, in more severe cases anti-inflammatory treatment may also be needed, requiring a specialised surgical team.[13]



BID = twice daily; DLQI = Dermatology Life Quality Index; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; OD = once daily; PGA = Physician Global Assessment; PO = orally

Figure 2. Treatment algorithm for HS based on the European guidelines.[13]

Is there a window of opportunity to treat HS?

Dr Rubel emphasised that early diagnosis and treatment is important in HS as it is associated with physical, emotional and psychological effects that can worsen. She emphasised the importance of educating GPs, other health care professionals and patients about HS in order to achieve better control of the disease early, and thus ensure better outcomes for patients.

Associate Professor Oakley agreed that there is an opportunity for improved outcomes when HS is diagnosed and treated early, but unfortunately patients presenting to dermatologists in the public health system often have severe disease. She pointed out that the PHARMAC Special Authority criteria for adalimumab in NZ supports early treatment with biologics for those with moderate-to-severe HS if previous therapies fail.[10] She stressed that early referrals for HS needs to be encouraged in the public health system. A challenge with referrals is that access to dermatology services varies throughout NZ.

Associate Professor Oakley discussed the dermatology referrals system in the Waikato DHB where they receive over 500 teledermatology referrals per month. A typical early teledermatology referral for HS would be followed by a non-contact first-specialist appointment and a 3-month course or doxycycline or similar would likely be recommended with follow-up images requested at the end of treatment. Depending on the patient's response to initial treatment, they may then be accepted for assessment in the clinic.

Dr Rubel explained that in her clinic she often sees patients with HS who have been misdiagnosed. Such patients include those that have been misdiagnosed with chronic infections and have ended up in the infectious diseases clinic, and patients referred to gynaecology, or surgery for removal of singular lesions. Patients are often treated between specialties such as gastroenterology, rheumatology and endocrinology due to their comorbidities. Ideally there would be a multidisciplinary team managing the HS patient.

TAKE-HOME MESSAGES

- HS is easy to diagnose but difficult to treat
- Risk factors for HS include obesity and smoking
- Comorbidities are often inflammatory
- A weight loss of 15% may result in less severe disease
- First-line therapy comprises antibiotics (usually doxycycline)
- Adalimumab has proven efficacy in HS.

QUESTION AND ANSWER SESSION:

Q. How do we differentiate between diagnosis of recurrent acne, HS or staphylococcal infection in young people?

A. **(AO)** Acne and staphylococcal infections affect different sites from HS. They can co-exist with HS.
(DR) Outbreaks of boils during the last 6 months with a minimum of two boils with five different location options (axilla, groin, genitals, under the breasts and other locations [not specified – e.g., perianal, neck, and abdomen]).

Q. Are there any features that help separate perianal CD diagnosis from perianal HS?"

A. **(AO)** There is overlap and diagnosis may depend on other sites of involvement or on biopsy.
(DR) This can be difficult. HS: presence of disease elsewhere, superficial lesions, comedones. CD: anal skin tags.

Q. I was surprised by the figure of up to 17% of CD patients having HS. This would not be our experience in Canterbury. Do you think that we are missing this or perhaps there is an overlap with perianal fistulising CD?

A. **(AO)** Both are probably true. As far as I know, there are no local prevalence studies examining CD and HS. I certainly have patients with both disorders and sometimes, recognition of HS has led to the diagnosis of CD.
(DR) HS may be subtle, in hidden areas, or undiagnosed.

Q. We have heard that referrals into some dermatology clinics can be difficult due to capacity – is there certain information a GP should definitely include in the referral letter for suspected HS to increase the chances of getting seen?

A. **(AO)** Public dermatology in New Zealand is in crisis. Describe the areas involved, the number of abscess and inflamed nodules, treatment that has been used, and attach photographs.
(DR) Number of inflammatory lesions and the number of sites involved.

Q. Some data you showed suggested HS patients often get misdiagnosed and inappropriately referred to the wrong specialist before they get to a dermatology clinic. What can be done to improve this problem, especially in light of the 'window of opportunity data' you showed?

A. **(AO)** This presentation is an example of an attempt to reach a broad range of practitioners with educational programmes in a variety of media.
(DR) Improving diagnosis by primary health care professionals and nurses – familiarity with the disease, typical presentation and sites of involvement. I find that once a GP has diagnosed HS in one patient, they rarely miss it subsequently.

REFERENCES:

1. Vazquez BG et al. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. J Invest Dermatol. 2013;133:97-103.
2. Goldburg SR et al. Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol. 2020;82(5):1045-1058.
3. Vinkel C et al. Hidradenitis suppurativa: Causes, features, and current treatments. J Clin Anesthet Dermatol. 2018;11(100:17-23.
4. Ngan V and Oakley A. Hidradenitis suppurativa. DermNet NZ 2015. Available from: https://dermnetnz.org/topics/hidradenitis-suppurativa/ (Accessed Oct 2020).
5. van der Zee HH et al. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. Br J Dermatol. 2010;162(1):195-197.
6. Vellaichamy G et al. Patient-reported outcomes in hidradenitis suppurativa. G Ital Dermatol Venereol. 2019;154(2):137-147.
7. Kirby JS et al. The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials. Br J Dermatol. 2020 Aug;183(2):340-348.
8. Kromann CB et al. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. Acta Derm Venereol. 2014;94(5):553-7.
9. Goldburg SR et al. Hidradenitis suppurativa: Current and emerging treatments. J Am Acad Dermatol. 2020;82(5):1061-1082.
10. Pharmac. Adalimumab Special Authority application. Available from: https://pharmac.govt.nz/ (Accessed Oct 2020).
11. Medsafe. Humira® data sheet. Version 5.0. Available from: https://www.medsafe.govt.nz/profs/Datasheet/h/humirainjpeninj.pdf (Accessed Oct 2020)
12. Zouboulis C et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol. 2019 Jan;80(1):60-69.e2.
13. Gulliver W et al. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016 Sep;17(3):343-351.

SIGNALLING PATHWAYS IN INFLAMMATORY DISEASE

– Professor Ernest Choy

Professor Ernest Choy

Professor Ernest Choy is Head of Rheumatology and Translational Research at the Institute of Infection and Immunity and Director of the Cardiff Regional Experimental Arthritis Treatment and Evaluation (CREATE) Centre at Cardiff University School of Medicine, Cardiff, Wales, UK. He is also Honorary Consultant Rheumatologist at University Hospital of Wales and Clinical Lead of the Welsh Arthritis Research Network (WARN). Previously, he was Reader and Director of Rheumatology, Kings College London. His major research interest is the treatment of rheumatic diseases, focussing on the efficacy of new treatment strategies. He was Director of Research and Development at King's College Hospital between 2003 and 2008. In 2007, he chaired the EULAR Taskforce on developing recommendations for management and classification criteria for fibromyalgia. He has also served as clinical expert to the National Institute for Clinical Excellence in the UK, and many pharmaceutical companies. He has published widely on treatments for rheumatic diseases in major medical journals such as the New England Journal of Medicine. He is a frequent lecturer on the treatment of rheumatic diseases.

Treatments for RA

Professor Choy explained that in many parts of the world there has been a dramatic increase in available treatments for rheumatoid arthritis (RA) during the previous two decades, with approval in the European Union for infliximab and etanercept in 2000, adalimumab in 2003, rituximab in 2006, abatacept in 2007, tocilizumab, golimumab and certolizumab in 2009, and tofacitinib in 2017. He pointed out that international RA guidelines have been frequently updated to reflect the availability of these new agents.

The aim for treatment in RA is to treat the right patient at the right time and this is becoming increasingly possible in a number of other diseases with the development of precision medicine involving the tailoring of treatment based on an individual's genetic and epigenetic predictors or `biomarkers' of therapeutic response.[1] Unfortunately this remains an unmet need in RA as satisfactory biomarkers have not yet been identified. In RA, rheumatoid factor and anti-CCP antibodies have been recognised for their potential as predictors of response, with patients positive for these markers responding better to treatment with rituximab than those who are negative.[2] However, differences in response between these two groups of patients were not compelling enough to assign these factors biomarker status.

Professor Choy and colleagues have recently demonstrated the heterogeneity of RA in a study of synovial pathobiological markers in treatment-naïve patients with early RA.[3] They found that patients exhibit very different underlying pathology driving the disease process and categorised these into three synovial histological groups: lympho-myeloid (lymphoid infiltration a dominant feature); diffuse myeloid (monocyte/macrophage infiltration dominant); and pauci-immune (very few inflammatory cells present).[3] The overlap and interplay between cytokines drives synovial inflammation in RA and the features identified in the three histological groups reflect complex interactions between T cells and B cells, macrophages, dendritic cells and synoviocytes, with the different immune cells and cytokines being less or more important in an individual patient's disease pathology.[4] According to Professor Choy, this is the reason patients respond differently to different therapies and is why we need an armamentarium of agents to treat RA.

Unmet needs in RA

The current goal of therapy in RA is remission as this lowers the likelihood of joint damage.[5] In order to optimally treat RA patients, we need to identify prognostic factors for disease development and progression, and identify predictors for treatment response. A second unmet need is the achievement of drug-free remission, which Professor Choy says is possible in early RA but less likely in established RA.

It is evident that even patients with stable disease activity experience flares in the form of isolated disease activity peaks followed by a return to previous levels.[6] Furthermore, a pooled analysis of three large observational studies (RA Impact of Disease [RAID], COMorbidities, EDucation in Rheumatoid Arthritis [COMEDRA] and the Coimbra RA cohort [CoimbRA]) has shown that patients experiencing low disease activity (near-remission) and no significant signs of inflammation still report significant pain, functional impairment, and disease impact (RAID and Patient Global Assessment scores) at levels similar to patients in non-remission.[7] We also know that in addition to joint pain, patients with RA often experience decreased pain thresholds in other non-articular regions.[8] Reductions in pain thresholds have been found to be highly positively correlated with tender joint counts, fatigue (Visual Analog Scale [VAS]), and disability (Health Assessment Questionnaire), and moderately associated with pain (VAS), depression and anxiety (Hospital Anxiety and Depression Scale), and patient global assessments.[8]

Targeting signal transduction

Professor Choy explained that advanced treatments for RA can be classified into three main groups. 1. Cytokine-targeting biologics including anti-TNFs (e.g., adalimumab, infliximab and golimumab), which block the TNF signalling pathways, and IL-6 inhibitors (e.g., tocilizumab), which block IL-6 receptor signalling pathways.[4] 2. Cell-targeting biologics that inhibit T-cells (e.g., abatacept), and deplete B-cells (e.g., rituximab).[4] 3. Small-molecule inhibitors such as Janus kinase (JAK) inhibitors that target signal transduction pathways.[4]

TAKE-HOME MESSAGES

- Satisfactory biomarkers have not yet been identified in RA
- RA patients exhibit very different underlying pathology driving the disease process and may be categorised into three synovial histological groups
- The current goal of therapy in RA is remission
- Advanced treatments for RA can be classified into three main groups: Cytokine-targeting biologics; Cell-targeting biologics that inhibit T-cells and deplete B-cells; Small-molecule inhibitors that target signal transduction pathways.

QUESTION AND ANSWER SESSION:

Q. Might there be a role to check rheumatological markers (rheumatoid factor or anti-CCP) routinely in patients with CD to determine whether they may respond better to methotrexate verses our usual 1st-line immunomodulator (azathioprine)?

A. As a Rheumatologist, I am not qualified to answer this, but I know there is ongoing work on biomarkers in CD.

Q. Do you see a time in the future where we will see more biomarker-driven treatment management in rheumatology, like we do in oncology?

A. This is my vision and our current research.

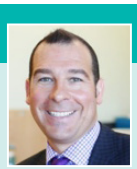
REFERENCES:

1. Plant D et al. Genetic and epigenetic predictors of responsiveness to treatment in RA. Nat Rev Rheumatol. 2014;10(6):329-37.
2. Chatzidionysiou K et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. Ann Rheum Dis. 2011;70(9):1575-80.
3. Lliso-Ribera G et al. Synovial tissue signatures enhance clinical classification and prognostic/treatment response algorithms in early inflammatory arthritis and predict requirement for subsequent biological therapy: results from the pathobiology of early arthritis cohort (PEAC). Ann Rheum Dis. 2019;78(12):1642-1652.
4. Choy EH et al. The problem of choice: current biologic agents and future prospects in RA. Nat Rev Rheumatol. 2013;9(3):154-63.
5. Vermeer M et al. Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: Three-year results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort. Arthritis Care Res (Hoboken). 2013;65(8):1219-26.
6. Dougardos M et al. Evaluation of the Disease Activity Score in twenty-eight joints-based flare definitions in rheumatoid arthritis: Data from a three-year clinical trial. Arthritis Care Res (Hoboken). 2015 Dec;67(12):1762-6.
7. Ferreira RJO et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford). 2017;56(9):1573-1578.
8. Pollard LC et al. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration. J Rheumatol. 2012;39(1):28-31

MAXIMIZING OUTCOMES WITH ANTI-TNF: TREATMENT STRATEGIES AND COST-EFFECTIVENESS

– Professor Remo Panaccione

Associate Professor Remo Panaccione



Associate Professor Remo Panaccione is the Director of the Inflammatory Bowel Disease Clinic and Director of the Gastroenterology Training Program in the Department of Medicine, University of Calgary, Canada. He is an internationally recognised expert in inflammatory bowel disease (IBD). His special interest lies in the implementation and performance of clinical trials of new therapies in IBD. He also performs research in identifying new targets to develop new therapies in IBD.

Professor Panaccione explained that there has been significant progress in the scientific understanding of diseases in the fields of gastroenterology, rheumatology and dermatology over the past years and this has led to the development of new targeted therapies. He pointed out that in various parts of the world, approvals are pending for a number of biologic therapies outside of anti-TNF therapy. With the armamentarium for treating a number of diseases expanding, we must understand how to use both old and new therapies in the best possible manner for maximal benefit.

Professor Panaccione pointed out that at the time of development and subsequent approval of anti-TNF for the management of IBD 25 years ago, there was a lack of understanding of the progressive nature of the disease, low levels of patient awareness and understanding of the burden of disease, no tools to measure cumulative damage and disability, no consensus on how to optimise treatment and monitor IBD patients, no consensus on how to optimise conventional treatment, no clear prognostic factors to identify patients for anti-TNF therapy, and no clear targets for IBD treatment. With a better understanding of the natural history of disease in IBD there has been an evolution in treatment strategies shifting away from simple control of symptoms towards full control of disease.[1] Key strategies for improving outcomes in IBD are shown in **Figure 3.**[1] Professor Panaccione pointed out that these strategies are equally important for rheumatological and dermatological diseases and that most clinicians have now adopted a treat-to-target (T2T) approach, monitoring disease on an ongoing basis for tight control. He stressed that these treatment strategies are the key to getting the most out of any drug therapy, as they effectively turbocharge their effectiveness.

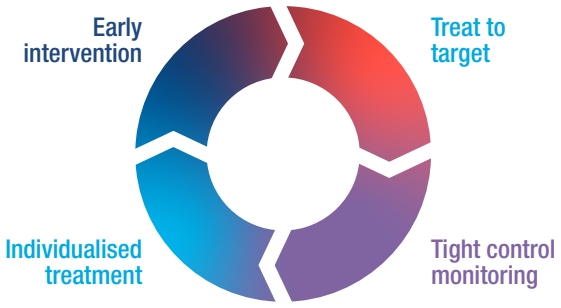


Figure 3. Key strategies for improving patient outcomes.(Adapted from Colombel et al., 2017)[1]

Early intervention

Professor Panaccione explained that prior to the biologics era, IBD patients were often only treated for disease flares and that repeated inflammatory activity often led to complications such as stricture, fistulae and abscesses requiring surgery.[2,3] He discussed the `window of opportunity' for treating IBD where the patient is treated early in the disease course before significant inflammation and damage, and that they are treated long-term, and noted that this is now the preferred strategy, particularly in CD.

An analysis of pooled data from 10 clinical trials of adalimumab in CD by Professor Panaccione and colleagues has shown that earlier initiation of adalimumab shortly after diagnosis leads to improved long-term clinical outcomes in patients with moderate-to-severe disease.[4] Similar findings have been shown in a real-world Korean study involving 670 patients with CD and poor prognostic factors that looked at early (within 2 years of CD diagnosis) versus late (>2 years) treatment with immunomodulators or anti-TNFs +/- immunomodulators.[5] Kaplan-Meier survival analysis revealed that patients treated early had significantly lower cumulative rates of intestinal surgery ($p < 0.001$), behavioural progression ($p < 0.001$), penetrating ($p < 0.001$) and stricturing complications ($p = 0.002$).[5]

Evidence for the `window of opportunity' for treatment has been shown in HS patients managed with adalimumab.[6] In a real-life multicentre cohort study involving 389 patients with HS from 21 Italian dermatology units, a `therapeutic delay' of ≥10 years from diagnosis correlated to lack of response with adalimumab in terms of HiSCR at week 16 (OR 1.92; 95% CI 1.28-2.89, $p = 0.0016$).[6]

Professor Panaccione emphasised that the concept of early treatment is also important in RA and ankylosing spondylitis, where the aim is to treat before any permanent damage to the joints develops, and that early treatment has the potential to reverse some existing damage.

Treat-to-target

Professor Panaccione explained that T2T is a concept that describes a change in therapeutic strategy from a symptom-driven to a target-driven approach and involves pre-defining a treatment target, monitoring disease activity tightly, modifying treatment until the target is reached and continuing to monitor and make adjustments. He stressed the importance of both the clinician and patient being willing to modify therapy based on the agreed target, even if the patient is asymptomatic. As an example, he discussed T2T in hypertension and diabetes, where patients may be asymptomatic but if the target blood pressure or HbA1c level is not reached, they are at risk of the complications that come with uncontrolled disease.

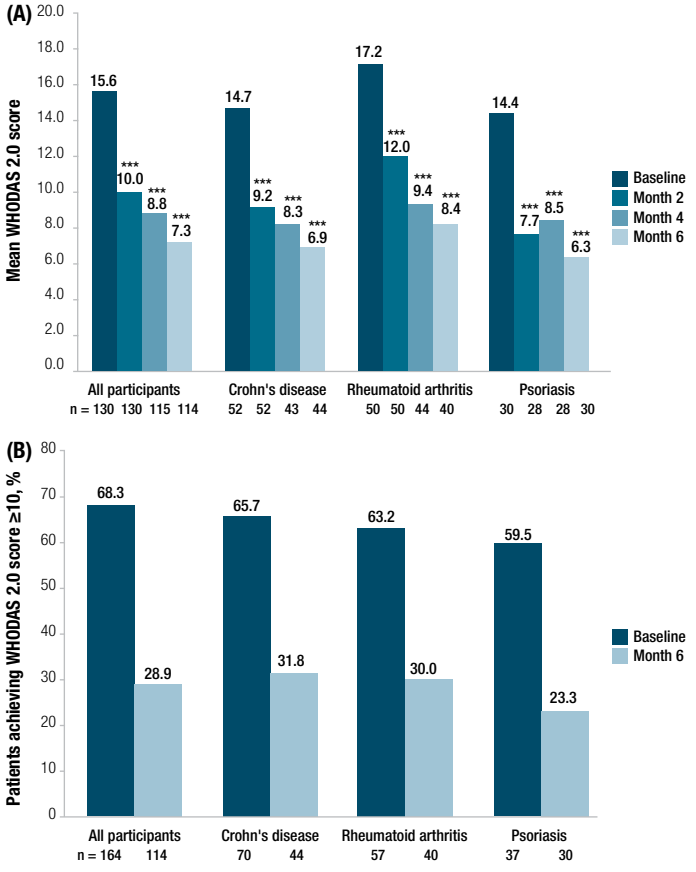
In IBD, new therapies have led to an evolution of treatment goals to facilitate greater disease control. Professor Panaccione pointed out that we can now aim for mucosal healing, deep remission and to change the course of disease by avoiding complications, rather than just symptom control, clinical remission or steroid-free remission. Several years ago, a Steering Committee of 28 IBD specialists, including Professor Panaccione, developed 12 recommendations for treatment targets in ulcerative colitis and CD to be used for T2T, resulting in a composite target of not only symptomatic remission but endoscopic remission (mucosal healing).[7] International RA guidelines, advocate a T2T approach and a target of sustained remission or low disease activity for every patient.[8,9] Professor Panaccione reported that unfortunately, uptake of T2T is not 100% across disease states, despite recommendations for its utilisation.

It is recognised that treatment goals may need to be different in late versus early disease.[3] Symptomatic remission may not be achievable in late-stage disease.[3] Patients with CD who are diagnosed late in their disease or who have already experienced a disease complication may not be able to achieve mucosal healing as a treatment goal.[3]

Evidence for improved outcomes with T2T

In RA, achieving remission is associated with improved physical function and work productivity according to the findings of an Austrian study involving 356 consecutive clinic patients.[10] Improvement in work productivity has also been demonstrated in patients treated with adalimumab for CD in the multicentre, observational PYRAMID post-marketing registry, with all 4 Work Productivity and Activity Impairment (WPAI) subscores (absenteeism, presenteeism, overall work impairment, activity impairment) meaningfully improved (absolute change in WPAI of >7%) at 1 to 6 years, with numerically greater WPAI scores in patients with disease duration <5 years versus ≥5 years.[11,12] Professor Panaccione commented that this study reinforces the importance of early intervention and demonstrates what is possible not only for the patient, but for society in terms of work productivity.

VITALITY, a 6-month, multicentre, prospective, observational study undertaken in NZ by Richard Gearry and colleagues has investigated the effects of adalimumab on health and disability outcomes in 164 patients with severe CD, RA or psoriasis.[13] The study looked at the impact of adalimumab on these patients and specifically the impact of treatment on their QoL.[13] A 50% reduction from baseline in mean World Health Organization Disability Assessment Schedule (WHODAS) 2.0 score was seen after 6 months of treatment with adalimumab across the whole cohort (5.2 points vs 7.3 points), with statistically significant improvements seen by 2 months ($p < 0.001$) (**Figure 4**).[13] A 50% reduction from baseline was also seen at 6 months in the proportion of patients with clinically significant disability (WODAS 2.0 score ≥10); 68.3% vs 28.9%.[13]



***p < 0.001 vs baseline, paired *t*-test

WHODAS = World Health Organization Disability Assessment Schedule

Figure 4. (A) Mean WHODAS 2.0 score over time in patients treated with adalimumab. (B) Proportion of participants treated with adalimumab with WHODAS 2.0 score ≥10 at baseline and 6 months.[13]

Tight control monitoring

The multicentre, open-label, randomised, controlled phase 3 CALM trial undertaken by Professor Panaccione and colleagues assessed 2 treatment algorithms, tight control and clinical management, in 244 patients with moderate-to-severe CD.[14] Need for escalation of treatment to increasing doses of adalimumab or adalimumab + azathioprine was assessed at 11, 23 and 35 weeks.[14] In the tight control group, treatment escalation was driven by failure criteria based on the Crohn's Disease Activity Index (CDAI), fecal calprotectin, C-reactive protein (CRP) and prednisone use, while in the clinical management group it was driven by the CDAI and prednisone use.[14] De-escalation of therapy was possible for patients on weekly adalimumab +/- azathioprine when failure criteria were not met.[14] At 48 weeks, the primary endpoint of mucosal healing (defined as a Crohn's Disease Endoscopic Index of Severity [CDEIS] <4) and no deep ulcers was achieved by significantly more patients receiving tight control than clinical management (46% vs 30%), with a Cochran–Mantel–Haenszel-adjusted risk difference of 16.1% (95% CI 3.9-28.3), p = 0.010.[14] The CALM trial emphasised that by measuring beyond symptoms and looking for markers of inflammation, appropriate therapy may be initiated and intensified earlier resulting in better outcomes for patients.

Professor Panaccione and colleagues analysed hospitalisation rates at week 48 in the CALM trial and identified rates of 13.2 per 100 patients-years in the tight-control group versus 28.0 per 100 patients-years in the clinical management group (p = 0.021).[15] A analysis of QoL outcome using in the CALM trial data revealed significantly greater improvements in SF-36, FACIT-F, PHQ-9, and the WPAI daily activity impairment subscore measures in the tight-control group when compared with the clinical management group.[16]

With the measurable benefits seen with tight control monitoring in CD, including reductions in hospitalisation rates, improved QoL and work measures, Professor Panaccione and colleagues sought to determine whether these factors may help to offset the financial costs of the agents used. Their cost-effective analysis used data from the CALM trial and costs reflective of a UK setting to determine direct medical costs (cost of hospitalisation, cost of adalimumab, other medical costs) and indirect costs (cost of missed work hours).[15] The analysis revealed that from a UK perspective a tight control approach to the management of CD with adalimumab was cost-effective compared with a clinical management approach.[15] Professor Panaccione reported similar findings when the data were applied to the NZ setting (AbbVie data on file).

Cost-effectiveness analyses of different T2T strategies have also been undertaken in RA (DREAM), psoriatic arthritis (TICOPA) and axial spondyloarthritis (TiCOSPA) and all demonstrate the cost-effectiveness of a T2T approach.[17-19]

TAKE-HOME MESSAGES

- Effective management of patients across a range of diseases including IBD, RA and psoriasis requires a T2T approach
- Optimal patient management involves early intervention, T2T, tight control monitoring and individualised treatment
- A T2T approach results in QoL benefits for patients
- The costs of anti-TNFs are off-set by a reduction of other direct medical costs and indirect costs.

REFERENCES:

1. Colombel J-F et al. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017;152(2):351-361.e5.
2. Pariente B et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011 Jun;17(6):1415-22.
3. Panaccione R et al. Evolving definitions of remission in Crohn's disease. Inflamm Bowel Dis. 2013;19(8):1645-53.
4. Panaccione R et al. Efficacy and safety of adalimumab by disease duration: Analysis of pooled data from Crohn's disease studies. J Crohns Colitis. 2019;13(6):725-734.
5. Oh EH et al. Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. PLoS One. 2017;12(5):e0177479.
6. Marzano AV et al. Evidence for a 'window of opportunity' in hidradenitis suppurativa treated with adalimumab: a retrospective, real-life multicentre cohort study. Br J Dermatol. 2020;Mar 2 [Epub ahead of print]
7. Peyrin-Biroulet L et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110(9):1324-38.
8. Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-977.
9. Lau CS et al. APLAR rheumatoid arthritis treatment recommendations. Int J Rheum Dis. 2015;18(7):685-713.
10. Radner H et al. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. Arthritis Res Ther. 2014;16(1):R56.
11. Loftus EV et al. Adalimumab effectiveness up to six years in adalimumab-naïve patients with Crohn's disease: Results of the PYRAMID Registry. Inflamm Bowel Dis. 2019;25(9):1522-1531.
12. Loftus EV et al. P757 Long-term effectiveness and safety of adalimumab based on Crohn's disease duration: Results from the PYRAMID registry. J Crohns Colitis 2018;12(Suppl 1):S493-494.
13. Gearry RB et al. VITALITY: impact of adalimumab on health and disability outcomes in patients with Crohn's disease, rheumatoid arthritis, or psoriasis treated in clinical practice in New Zealand. Curr Med Res Opin. 2019;35(10):1837-1846.
14. Colombel J-F et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. Lancet. 2017;390(10114):2779-2789.
15. Panaccione R et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: An economic assessment of the CALM trial. Gut. 2020;69(4):658-664.
16. Panaccione R et al. DOP071 Tight control with adalimumab-based treatment is associated with improved quality of life outcomes in patients with moderate to severely active Crohn's disease: data from CALM. J Crohns Colitis 2018;12(Suppl 1):S078-S079.
17. van de Laar CJ et al. Cost-effectiveness of different treat-to-target strategies in rheumatoid arthritis: results from the DREAM registry. BMC Rheumatol. 2019;3:16.
18. Coates LC et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386(10012):2489-98.
19. Moltó A et al. THU0370 Cluster-randomised pragmatic clinical trial evaluating the potential benefit of a tight-control and treat-to-target strategy in axial spondyloarthritis: The results of the TICOSPA trial. Annals Rheum Dis. 2020;79(Suppl 1):417.

SUBSCRIBE FREE!

Helping New Zealand health professionals keep up to date with clinical research

RHEUMATOLOGY RESEARCH REVIEW

This Review features key medical articles from global journals with commentary from Associate Professor Simon Stebbings and Associate Professor Andrew Harrison.

The Review covers topics such as lupus, psoriatic arthritis, juvenile arthritis, inflammatory arthritis, ankylosing spondylitis, NSAIDs, COX-2 inhibitors, anti-TNF drugs, monoclonal antibodies and joint replacement surgery.

DERMATOLOGY RESEARCH REVIEW

This Review features key medical articles from global Dermatology journals with commentary from Dr Louise Reiche. The Review covers topics such as psoriasis, acne, vitiligo, rosacea and dermatitis.

IBD RESEARCH REVIEW

This Review features key medical articles from global gastroenterology journals with commentary from Professor Michael Schultz, Dr Srikantaiah Manjunatha and Christine Ho.

The Review covers topics such as Crohn's disease, ulcerative colitis, colonscopy, colitis, inflammatory bowel disease, biological drugs, and tumour necrosis factor (TNF) inhibitors.

SUBSCRIBE FOR FREE AT

www.researchreview.co.nz

RESEARCH REVIEW™
Making Education Easy — Since 2006

PHARMAC Pharmaceutical Schedule: HUMIRA is fully subsidised under Special Authority for the treatment of patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, severe chronic plaque psoriasis, juvenile idiopathic arthritis, severe or chronic ocular inflammation (uveitis) and hidradenitis suppurativa. Refer to the Pharmaceutical Schedule for full Criteria. HUMIRA is not funded for ulcerative colitis, non-radiographic axial spondyloarthritis and enthesitis-related arthritis.

Please review full Data Sheet before prescribing. Full Data Sheet is available on request from AbbVie Limited by calling 0800 900 030, or on the Medsafe website at www.medsafe.govt.nz/profs/datasheet/h/humirainjpeninj.pdf HUMIRA is a Prescription Medicine containing adalimumab 20 mg/0.4 mL or 40 mg/0.8 mL for injection.

INDICATIONS:
Rheumatoid Arthritis (RA): Reducing signs & symptoms, and inhibiting the progression of structural damage, in adults with moderate to severely active RA; including patients with recently diagnosed moderate to severely active disease who have not received methotrexate. HUMIRA can be used alone or in combination with methotrexate.

Polyarticular Juvenile Idiopathic Arthritis (pJIA): in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active pJIA in patients aged 2 years of age and older. HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis (ERA): Treatment of ERA in patients, 6 years of age and older, with an inadequate response, or intolerance to, conventional therapy.

Psoriatic Arthritis (PsA): Treatment of signs and symptoms, and inhibiting the progression of structural damage, of moderate to severely active PsA in adult patients with inadequate response to DMARDS.

Ankylosing Spondylitis (AS): Reducing signs and symptoms in patients with active AS.

Non-radiographic Axial Spondyloarthritis (nr-axial SpA): Treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

Crohn's Disease (CD) in Adults and Children (≥6 years): Treatment of moderate to severe CD, to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients with; inadequate response to conventional therapies or, who have lost response to, or are intolerant to, infliximab.

Ulcerative Colitis (UC): Treatment of moderately to severely active UC in adult patients with intolerance, medical contraindication, or inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA).

Psoriasis in Adults and Children (≥ 4 years): Treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Treatment of severe chronic plaque psoriasis in children and adolescent patients from 4 years of age, with an inadequate response to, or are inappropriate candidates for, topical therapy and phototherapy.

Hidradenitis Suppurativa (HS) in Adults and Adolescents (≥ 12 years): Treatment of active moderate to severe HS (acne inversa) in patients with an inadequate response to conventional systemic HS therapy.

Uveitis: Treatment of non-infectious intermediate, posterior and pan-uveitis in adult patients with inadequate response to corticosteroids, those in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis (≥ 2 years): Treatment of paediatric chronic non-infectious anterior uveitis, in patients with inadequate response, or intolerance to conventional therapy, or in whom conventional therapy is inappropriate.

CONTRAINDICATIONS:
Severe infections including sepsis, active tuberculosis, opportunistic infections; concurrent anakinra administration; moderate to severe heart failure (NYHA class III/IV); known hypersensitivity to HUMIRA or its excipients.

PRECAUTIONS:
Infections (bacterial, mycobacterial, invasive fungal e.g, histoplasmosis, viral or other opportunistic); hepatitis B, TB (reactivation, new onset or latent); demyelinating disorders* (central or peripheral; neurologic evaluation required prior to initiation and ongoing for patients with intermediate uveitis); haematologic events; live vaccines; immunosuppression; new or worsening CHF; renal, hepatic impairment; malignancy; hypersensitivity reactions; autoimmune processes (auto-antibodies, lupus-like syndrome); use in psoriasis with phototherapy; concurrent biologic DMARDs or other TNF antagonists; elderly; pregnancy, lactation, surgery. *Refer to Data Sheet under Neurologic Events.

ADVERSE REACTIONS:
Respiratory tract infections, leukopaenia, anaemia, lipid increase, headache, abdominal pain, nausea and vomiting, elevated liver enzymes, rash, musculoskeletal pain and injection site reaction are very commonly seen adverse events. Benign neoplasm and skin cancer including basal cell and squamous cell carcinoma were commonly reported. Fatal infections such as TB and invasive opportunistic infections have rarely been reported. For others, see full Data Sheet.

DOSAGE & ADMINISTRATION:
HUMIRA doses are to be administered by subcutaneous injection. Refer to the Data Sheet for full dosing instructions.

RA, PsA, AS and nr-axial SpA: 40 mg fortnightly as a single dose.

pJIA & ERA: Paediatric Patients (≥2 years for pJIA, ≥6 years for ERA)

10 kg to <30 kg = 20 mg fortnightly; ≥30 kg = 40 mg fortnightly.

CD and UC (Adults): Induction: 160 mg on Day 0 (given in one day or as 80 mg per day for two consecutive days), followed by 80 mg on Day 14. Maintenance: 40 mg starting on Day 28 and continuing fortnightly.

pCD: Paediatric Patients ≥6 years:
(Moderate to Severe CD) < 40kg – Induction: 80 mg on Day 0, followed by 40 mg on Day 14. Maintenance: 20 mg starting on Day 28 and continuing fortnightly.
(Moderate to Severe CD) ≥ 40kg – Induction: 160 mg on Day 0 (given in one day or as 80 mg per day for two consecutive days), followed by 80 mg on Day 14. Maintenance: 40 mg starting on Day 28 and continuing fortnightly.

Psoriasis & Uveitis (Adults): Initial dose of 80 mg, followed by 40 mg fortnightly, starting one week after the initial dose.

Paediatric Plaque Psoriasis (≥4 years): Induction: Doses to be given weekly for the first two doses, **then** Maintenance: continuing fortnightly. Dose based on body weight: < 30kg = 20 mg; ≥ 30kg = 40 mg.

HS (Adults): Induction: 160 mg on Day 1 (given in one day or as 80 mg per day for two consecutive days), followed by 80 mg on Day 15. Maintenance: 40 mg starting on Day 29 and continuing weekly or 80 mg fortnightly.

HS (Adolescents ≥12 years, weighing ≥ 30kg): Induction: 80 mg at Week 0. Maintenance: 40 mg fortnightly, starting at Week 1.

Paediatric Uveitis (≥ 2 years): Dose based on body weight. An initial loading dose may be administered one week prior to start of maintenance therapy. Refer to Data Sheet for doses and considerations.
Maintenance: < 30kg = 20mg fortnightly in combination with methotrexate;
≥ 30kg = 40mg fortnightly in combination with methotrexate.

DATE OF PREPARATION: June 2020, based on Data Sheet last updated 18 June 2020. Version 37a. AbbVie Limited, 6th floor, 156-158 Victoria Street, Wellington, 6011, New Zealand 0800 900 030

TAPS PP6956. NZ-HUM-200098. Prepared Nov 2020.

abbvie

This publication has been created with an educational grant from AbbVie. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of AbbVie. Treatment decisions based on these data are the full responsibility of the prescribing healthcare professional. All trademarks mentioned in this review are the property of their respective owners.