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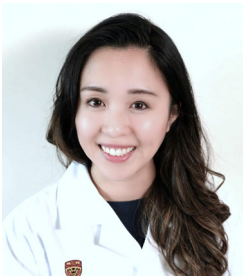

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Update on Lupus Nephritis

Christine A. Peschken, MD, MSc, FRCPC

Abstract

Lupus Nephritis (LN) is a common and severe manifestation of systemic lupus erythematosus (SLE), impacting up to 40% of SLE patients. Despite advancements in understanding the pathogenesis of LN, outcomes have not significantly improved since the early 2000s. LN patients face higher mortality, emphasizing the importance of achieving disease remission. Screening for nephritis involves regular monitoring, especially within the first 5 years of SLE diagnosis. Monitoring includes urinalysis, serum creatinine, and immune serology. Kidney biopsy remains the gold standard for LN diagnosis and classification, providing crucial information for treatment decisions. The standard of care involves hydroxychloroquine for all LN patients, with immunosuppressive treatments tailored to the histologic class. The recently approved medications, belimumab and voclosporin, offer additional therapeutic alternatives. Approximately 20% of LN patients exhibit features of thrombotic microangiopathy, warranting anticoagulation. Optimizing glucocorticoid dosing is recommended, favouring lower doses to minimize adverse effects. Lifelong monitoring is essential, as flares can occur at any point, emphasizing the need for continued immunosuppression.

Given the lack of renal response in 30–60% of patients, the addition of combination therapies, such as calcineurin inhibitors or belimumab, should be considered. Duration of treatment is crucial, considering the progressive loss of podocytes and nephron function, which may lead to chronic kidney disease. Regular monitoring, maintenance immunosuppression, and lifestyle modifications contribute to preventing flares and improving long-term outcomes for LN patients.

Introduction

LN is a severe and relatively common manifestation of systemic lupus erythematosus (SLE), affecting as many as 40% of SLE patients, with marked ethnic variations.[1] Approximately 10% of LN patients progress to end stage kidney disease (ESKD) within 10 years of diagnosis,[2] with higher rates for International Society of Nephrology (ISN) Class IV LN, reported at up to 44% progression at 15 years.[3] Patients with LN also have higher mortality; one large study of an inception cohort of 1827 new SLE patients showed an adjusted hazard ratio of death at 10 years of 3.2 for patients with LN versus those without LN.[4] Is important to note that mortality improves substantially if disease remission is achieved.[5]

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References: 1. TREMFYA®/TREMFYA ONE-PRESS® (guselkumab injection) Product Monograph. Janssen Inc. January 17, 2024. **2.** Alberta Health. Drug benefit list. Formulary Search Results. October 13, 2023. **3.** Manitoba Pharmacare. Manitoba Drug Benefits Formulary Bulletin #129. December 21, 2023. **4.** New Brunswick (NB) Drug Plans Formulary Update. Bulletin #1122. December 18, 2023. **5.** Newfoundland and Labrador Prescription Drug Program Bulletin #234. December 13, 2023. **6.** Nova Scotia Formulary November 16, 2023. **7.** Ontario Ministry of Health. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. December 18, 2023. **8.** Health PEI. PEI Pharmacare Formulary. November 2023. **9.** Saskatchewan Drug Plan. Formulary Search Results. November 16, 2023. **10.** Non-Insured Health Benefits (NIHB) Program. Drug Benefit List. November 30, 2023.

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Although our understanding of the pathogenesis of LN has improved, these outcomes have not improved substantially since approximately 2000. The Euro-Lupus trial, published in 2002, demonstrated the effectiveness of low-dose intravenous cyclophosphamide treatment for proliferative nephritis.[6] In 2009, the Aspreva Lupus Management Study showed no difference in remission induction between mycophenolate and monthly intravenous cyclophosphamide.[7] The ensuing changes in the LN treatment paradigm resulted in reduced treatment related adverse events but did not improve remission rates. For many patients with LN, a complete renal response, and even a partial response, remains elusive. The recent approval of two new medications for LN, with several more promising options in the pipeline, has reinvigorated the discussion on management of LN.

Screening Systemic Lupus Erythematosus Patients for Nephritis

LN can occur at any time during the patient's disease course; however, the highest risk is during the first 5 years after diagnosis. Early diagnosis of LN can improve outcomes. Patients should also be educated about the symptoms of LN, such as general malaise, hypertension, and edema. Thus, screening and monitoring for LN should continue throughout SLE, but should be performed more frequently, ideally every 3 to 6 months for the first 5 years after diagnosis and at least annually thereafter. Screening is completed through a number of tests, including urinalysis, serum creatinine, spot urine protein/creatinine ratio (uPCR) or albumin/creatinine ratio (uACR) and immune serology (dsDNA and complement levels).[8]

Kidney Biopsy

Traditional biomarkers that are used to assess lupus activity include complement levels (C3, C4), anti-dsDNA antibody levels, hematuria, proteinuria, and serum creatinine, including screening for LN as mentioned above, often do not correlate well with activity or diagnosis on kidney biopsy. Despite longstanding attempts to find serum or urine biomarkers to replace kidney biopsy, none have been validated or shown to be of adequate specificity and sensitivity. Kidney biopsy remains the gold standard for diagnosis, histological classification, and assessment of the severity of LN.[2,9]

Referral for biopsy should be considered if the patient experiences an abnormal or sustained reduction in the estimated glomerular filtration rate (eGFR), persistent and significantly elevated proteinuria (≥500 mg/day) and/or urinalysis with persistent proteinuria or hematuria that cannot be explained by an alternate etiology. A multidisciplinary approach including rheumatology and nephrology is recommended.[8,10]

LN is grouped into six histological classes based on the type of glomerular lesions observed[11] **(Table 1)**. In addition to determining the histologic class, and confirming the diagnosis of LN, kidney biopsy can help to determine activity and chronicity. Alternative diagnoses can be confirmed or ruled out, and additional features that influence the prognosis of LN can be determined, such as thrombotic microangiopathy, podocytopathy, and tubulointerstitial lesions. These biopsy findings will help to determine the appropriate monitoring and treatment.[10]

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis (< 50% of glomeruli)
Class IV	Diffuse proliferative lupus nephritis (≥50% of glomeruli)
Class V	Membranous lupus nephritis*
Class VI	Advanced sclerosing lupus nephritis (≥90% of glomeruli globally sclerosis without residual activity)

Table 1: Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of Lupus Nephritis; courtesy of Christine A. Peschken, MD, MSc, FRCPC
*Class V may occur in combination with class III or IV, in which case both will be diagnosed Indicate and grade (mild, moderate, severe tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

It is important to note that the lack of a biopsy should not substantially delay LN treatment. If a biopsy cannot be obtained in a timely fashion, or is contraindicated, consideration should be given for initiating treatment for LN in SLE patients who have convincing signs and symptoms of LN such as a decline in eGFR, persistent proteinuria >500 mg/day, hematuria on urinalysis, and the absence of an alternative explanation.

Standard of Care Treatment

All patients with LN should be treated with hydroxychloroquine unless there are contraindications. Hydroxychloroquine has been shown to improve LN outcomes, reduce LN flares, and delay progression to ESKD.[12]

Immunosuppressive treatment for LN depends on the histologic class and other biopsy features in addition to non-renal lupus activity. Class I and II LN may or may not require immunosuppressive treatment; this is based on levels of proteinuria and/or eGFR as well as other symptoms of lupus.

For Class III or IV LN, with or without a component of membranous nephritis (Class V), the standard of care (SoC) induction therapy includes mycophenolate or low dose intravenous cyclophosphamide, combined with high dose glucocorticoids (see previous page).[13,14] The choice of mycophenolate versus low dose cyclophosphamide is guided by individualized patient and physician discussions. High dose monthly intravenous cyclophosphamide (0.5–1 mg/m^2 body surface area) can be considered for those patients who are at high risk for renal failure (defined as a reduced eGFR, the histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), or for those with life-threatening disease.[14]

Data remain limited on the treatment of isolated Class V LN. Treatment choices will depend on the level of proteinuria and associated symptoms. For those patients requiring treatment, mycophenolate mofetil is recommended at the same doses as in Class III/IV disease, with calcineurin inhibitors, (particularly tacrolimus) either alone or in combination with mycophenolate mofetil as recommended alternatives.[10]

Class VI LN does not respond to immunosuppression; thus, treatment includes kidney replacement therapy.

Following treatment initiation, patients should be monitored every one to two months for renal response and adverse effects. Treatment targets include a reduction in proteinuria of ≥25% at 3 months and ≥50% at 6 months respectively, and below a level of 500–700 mg/day at 12 months, all while maintaining the eGFR within 10% from baseline.[14] For those not achieving these responses, treatment with the alternative SoC therapy (cyclophosphamide or mycophenolate) should be considered. High dose intravenous cyclophosphamide can also be considered. Combination therapy with belimumab, or calcineurin inhibitors (CNIs) should also be considered if they were not initiated earlier (see previous page). Rituximab can also be considered for refractory disease.[14] Some crucial factors should be considered prior to changing therapy, including adherence to therapy, adequate dosing, and alternative pathology. A repeat renal biopsy may be indicated. Multidisciplinary care with involvement of nephrology is recommended.

New and Additive Treatments

Recent studies have shown that 30% to 60% of patients fail to achieve either a complete or partial renal response. This represents a substantial unmet need in the treatment of LN. The approval of belimumab and voclosporin specifically for LN, after more than 20 years without new therapies, represents an important advance in the field. At the time of writing, belimumab has been approved in Canada, although its access remains limited, and voclosporin has not yet received Health Canada approval. However, there is optimism that access to new and upcoming treatments will improve and it is worthwhile to review their place in the treatment paradigm.

> ***All patients with LN should be treated with hydroxychloroquine unless there are contraindications.***

Voclosporin is more potent than cyclosporine and may cause less hypertension and hyperlipidemia compared to cyclosporine, and may cause less diabetes compared to tacrolimus. Voclosporin has not, however, been directly compared to either of these medications. In phase 3 trials, voclosporin, along with mycophenolate and oral corticosteroids, was shown to significantly improve renal response rates at 52 weeks. These results add to the encouraging literature on CNIs

for treating LN. Tacrolimus as monotherapy, or in combination with mycophenolate, has been shown effective in LN, and the combination has been shown to be superior to intravenous cyclophosphamide for induction therapy in the treatment of LN.[13,14] In the phase 3 LN study that evaluated belimumab, patients received belimumab on a background of SoC therapy. The study demonstrated that a significantly greater number of patients achieved both complete and partial renal response compared to placebo. Flare rates were also reduced, as was the risk of a renal-related event or death.[2]

Addition of a CNI (tacrolimus) to SoC therapy may be a good choice for patients with high levels of proteinuria, and relatively preserved renal function (eGFR >45 mL/min), while the addition of belimumab may be a good choice for patients with severe disease, at high risk of flare or relapse, and for those with a lower eGFR. Neither voclosporin nor belimumab have shown a clear benefit for Class V LN.[15]

While access to and cost of medications, adverse effects, and medication burden are all important and may influence therapeutic decisions, the significant number of patients who do not achieve renal response with SoC therapy suggests that the addition of combination therapy could be actively considered for all LN patients at the onset of treatment. If not added at the onset, failure to meet treatment targets at three months could prompt the addition of combination therapy.

Glucocorticoid Dosing in Lupus Nephritis

The recently updated and published EULAR recommendations for the management of SLE/LN support the use of lower doses of glucocorticoids, as did the 2019 EULAR guidelines for LN.[13,14] Glucocorticoids have both genomic and non-genomic effects. The genomic effects depend on intracellular receptors and alter the expression of pro-inflammatory and immunoregulatory genes. Glucocorticoid receptors are almost fully saturated at an approximately 30 mg/day prednisone equivalent. Higher doses result in further immunosuppression through non-genomic effects. These mechanisms support the suggested strategy of short-term high dose methylprednisolone followed by more moderate doses of oral prednisone.[15]

Pulses of intravenous methylprednisolone are recommended as part of the induction treatment for LN, unless there are concerns for

Treatment of LN Traditional	Drugs	Trends
Steroid pulse	• Steroid pulse • Oral prednisone 1 mg/kg	• May or may not be necessary • Dose and number of days may vary • Trend is less dose and more rapid taper
Hydroxychloroquine	5mg/kg/day	Adjust for some comorbidities
Immune suppression	MMF (i.e. 3g/day) or cyclophosphamide (i.e. 500 mg IV Q2w x 6 doses)	Consider MMF initially for many patients due to equal benefit and more safety
Added immune suppression	Belimumab CNI Other (other drugs in RCTs)	Trend is to consider upfront addition of one of these drugs to MMF or cyclophosphamide vs. Add if an outcome is not achieved at a specific time
Special circumstances	Pregnancy – use azathioprine and consider planning conception only when patient is under excellent control	Consider use of a SGLT2 inhibitors (gliflozins or flozins) for renal protection

Table 2. Trends in the approach to LN tretament; courtesy of Christine A. Peschken, MD, MSc, FRCPC

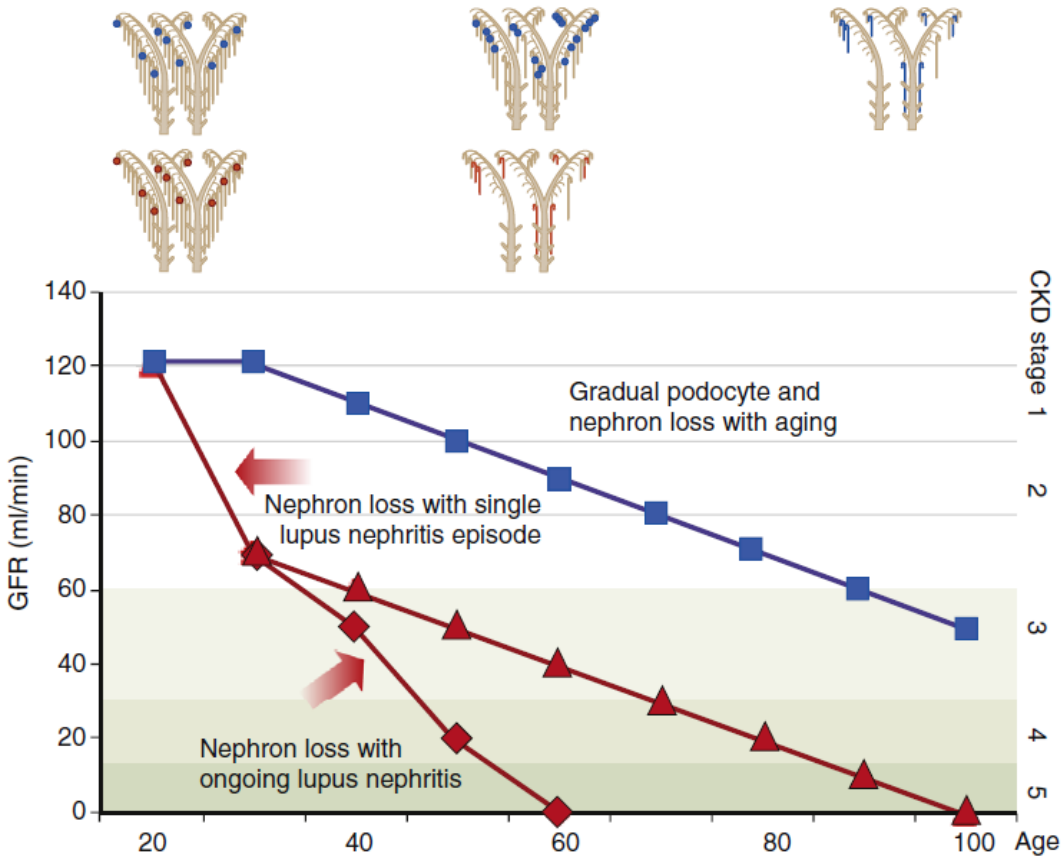

Figure 1. Nephron loss in lupus nephritis; adapted from Rovin et al, 2016. Anders HJ, Rovin B. A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis. Kidney Int. 2016;90(3):493-501.

infection, with a suggested dosing range of 250–1000 mg for 1–3 days. However, some authorities are suggesting no more than a dose of 1–1.5 g of methylprednisolone in total over 3 days,[15] advocating that benefit does not increase while infection risk does. Subsequent oral glucocorticoid doses are recommended at doses of 0.3–0.5 mg/kg/day (Class III/IV) and 20 mg/day (Class V) prednisone equivalent with a rapid taper to ≤5 mg/day.[14]

Additional considerations: Approximately 20% of LN biopsies will show features of thrombotic microangiopathy (TMA), with increased rates observed in the presence of antiphospholipid antibodies. TMA is associated with a worse prognosis. Data on treatment are lacking, although anticoagulation therapy is recommended. TMA should also be considered in the event of a non-response or a plateauing response to initial treatment, or flares, particularly in the absence of changes in standard biomarkers such as dsDNA, complement levels, or proteinuria.[14] **Table 2** on the previous page shows some trends with LN treatment.

Duration of Treatment and Flare Prevention

It is important to keep in mind that there is no cure for SLE. Flares and reactivation may occur at any point in the disease course, and lifelong monitoring for disease activity and flares is necessary. In adults, the continuous age-related loss of podocytes contributes to focal-segmental and later focal-global glomerulosclerosis, leading to an increased risk of chronic kidney disease in the elderly. A single episode of LN can result in significant podocyte and nephron loss, accelerating this risk. Repeated episodes or poor control of LN activity further accelerates nephron loss, increasing the likelihood of ESKD. With the loss of nephrons, the remaining nephrons undergo hypertrophy. As a result, eGFR may overestimate the number of nephrons; thus, a mildly increased serum creatinine may not accurately reflect the extent of nephron loss **(Figure1)**.[16]

These dual concepts emphasize the importance of an adequate duration of treatment and vigilance in preventing flares. Regular

monitoring for LN activity and progression, an appropriate duration of maintenance immunosuppression as above, and continuation of hydroxychloroquine and/or belimumab may all contribute to the prevention of flares. In the event of a flare, a repeat kidney biopsy is commonly indicated to assess for class switching, chronicity, and need for treatment.

Continuation of immunosuppression is recommended for at least three years following renal response. If the initial treatment was with mycophenolate, with or without CNIs or belimumab, these treatments should be continued. If treatment was initially with cyclophosphamide, this should be replaced with mycophenolate or azathioprine. In addition, azathioprine is preferred in patients considering pregnancy or in those who are intolerant to mycophenolate. A gradual withdrawal of immunosuppressive therapy may be considered following at least three years of treatment. Glucocorticoids should be withdrawn first followed by tapering of immunosuppressive drugs.[14] Hydroxychloroquine should be continued indefinitely unless contraindicated. While long-term data on the continuation of belimumab for LN is lacking, data on flare prevention, overall safety profile, and prevention of organ damage support long-term continuation if used initially.

Additional Treatment

Supportive therapies and lifestyle modifications to improve LN outcomes and reduce treatment and disease related comorbidities and adverse events are important. Antihypertensive therapy with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be considered in patients with proteinuria and/or hypertension. Statin medications to lower lipid levels may be indicated in some patients. Appropriate immunizations to reduce the risks of infection are imperative. Prevention of osteoporosis with calcium and vitamin D supplementation with or without bisphosphonate therapy should be considered.

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Sjogren's Syndrome: Strategies for Treatment

Arthur A.M. Bookman, MD, FRCPC

Introduction

Sjogren's syndrome, characterized by dry eyes, dry mouth, and immunological hyperactivity, has been one of the most difficult rheumatic diseases to differentiate and define. After many hours of consensus group development, studies on large cohorts/registries of over 1500 patients in totality and following national, European, American, and finally consensus iterations, criteria have been agreed upon for the classification of this disease. In the final analysis, these criteria are objective and accessible for measurement, and a number of them can be documented in clinical practice. To treat Sjogren's syndrome effectively, it is important to rely upon objective evidence with respect to the diagnosis of this disease, as well as the specific component of the condition that one is attempting to manage.

In this respect, Sjogren's syndrome is perhaps best confirmed by attempting to match the patient's findings with the 2016 ACR-EULAR Classification Criteria **(Table 1)**.[1] While these criteria are not meant for diagnosis but rather for the identification of confirmed cases for recruitment into clinical trials, they do exhibit a specificity of 95%, with a confidence interval (CI) of 92–97%, and a sensitivity of 96%, with a CI of 92–98%. It is important to note that high sensitivity is needed to correctly identify individuals with the condition. It is also important to note that many rheumatologists do not order a minor salivary gland biopsy and do not do a Schirmer's test or salivary flow rate. Patient history and physical examination along with a positive antinuclear antibody (ANA) and SSA (Ro) and/or SSB (La) accompanied by the presentation of dry eyes and mouth, may result in a clinical diagnosis of

Sjogren's syndrome being made, especially if there is Raynaud's phenomenon, gland swelling (parotids or submandibular) and/or leucocytoclastic vasculitis.

In clinical practice, many Sjogren's syndrome patients present with complaints of dry eye or dry mouth. One of the first questions that the practitioner must ask, is how reliable are these complaints? In our assessment of 385 patients with primary Sjogren's Syndrome,[2] we found that the correlation coefficient between the severity of complaints of dry eye measured by Visual Analog Score (VAS) and the measurement using the Schirmer's test was very poor at r=0.20. Correlation of these complaints with Rose Bengal or Lissamine Green staining for ocular surface dryness (van Bijsterveld Score) was even worse at r=0.18. It is important to keep in mind that correlation coefficients indicate more reliability as they approach r=1.

The classification of primary Sjogren's syndrome applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score of >4 when the weights from the 5 criteria items below are summed.

Item	Weight/ score
1. Labial salivary gland with focal lymphocytic sialadenitis and a focus score of >1 foci/4 mm^2	3
2. Anti-SSA/Ro positive	3
3. Ocular Staining Score >5 (or van Bijsterveld Score >4) in at least 1 eye	1
4. Schirmer's test <5 mm/5 minutes in at least 1 eye	1
5. Unstimulated whole saliva flow rate <0.1 mL/minute	1

Table 1. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome
Abbreviations: SSA/Ro, Sjogren's syndrome-related antigen A autoantibodies

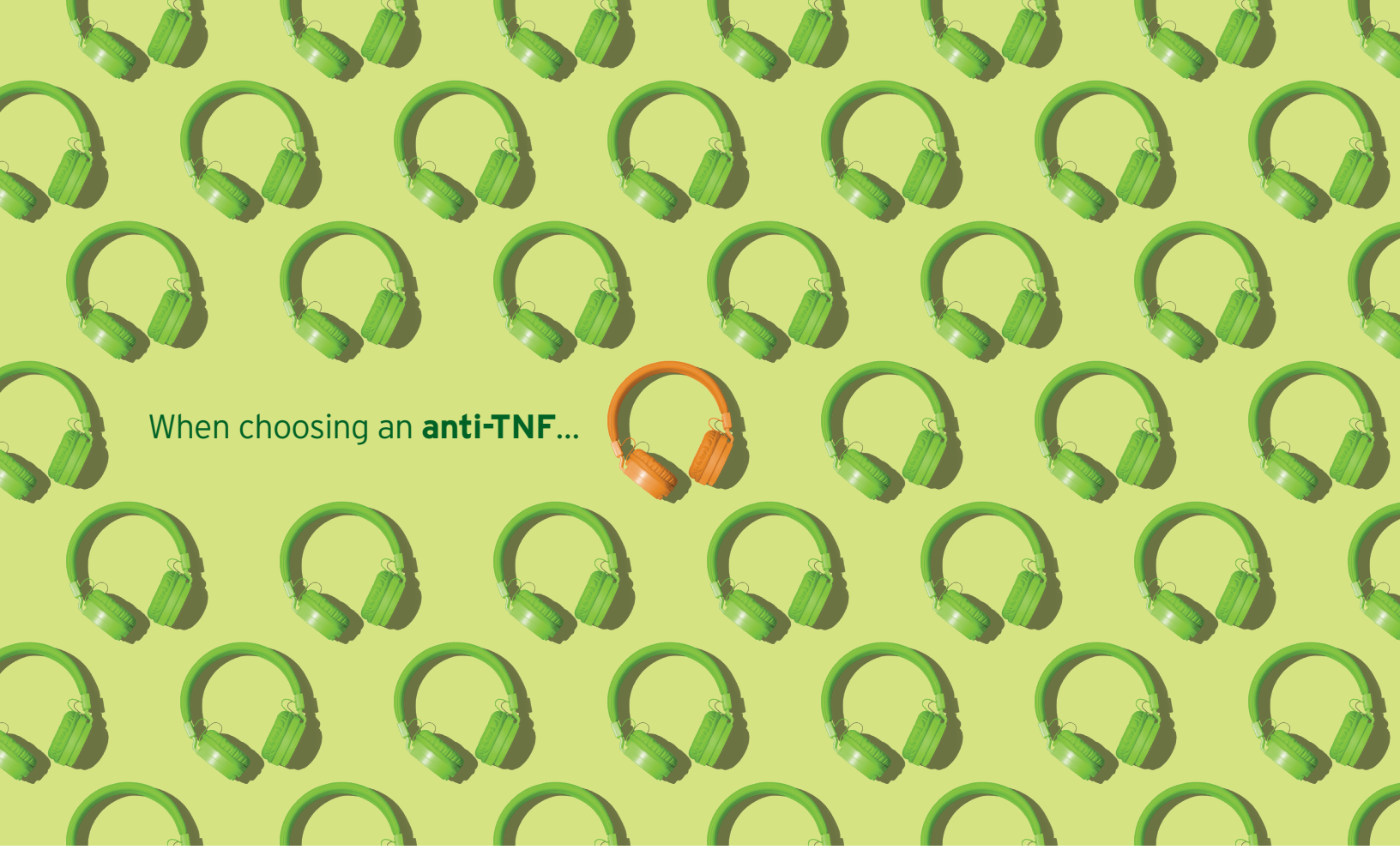
Correlation of perceived dry mouth severity as measured by VAS with the measurement of unstimulated whole salivary flow was only marginally better at r=0.29. It may be of interest to note that even though the correlation was poor between perceived and measured dryness, in patients with Sjogren's syndrome, the correlation was significantly better than in patients without Sjogren's who had sicca complaints (controls).

This study demonstrates the importance of objective measurement in office practice rather than relying on patient complaints. In the office, a complaint of dry eye can be confirmed with a Schirmer's test and a complaint of dry mouth can be confirmed with unstimulated salivary flow. Saliva can be collected in a specimen cup for a 5-minute period. The sample is then quantified by aspirating the cup contents into a 3 mL disposable syringe with a 20-gauge needle. The volume of saliva produced should be expressed as millilitres per minute.

These aspects of the Classification Criteria can be performed in any outpatient setting. Furthermore, the ability to measure anti-SSA antibody levels in any community laboratory allows for the identification of a large proportion of patients without resorting to other subspecialists such as ophthalmologists or ENT specialists for confirmation. The Ocular Staining Score (or van Bijsterveld Score) and minor salivary gland biopsy must be performed by other specialists when the objective dryness and anti-SSA antibody test results are insufficient to meet the criteria. A single test is not sufficient to confirm a diagnosis.

Treating Dry Eyes

When treating dry eye, it is important to conduct the Schirmer's test first. If the Schirmer's test result is normal, then the complaint of dry eye is often due to meibomian gland dysfunction. These glands line the closure surface of the upper and lower eyelids where they meet. They secrete oil that forms a major sandwich layer of the tear film along with water, to ensure that liquid uniformly coats the cornea and the rest of the eye. With meibomian gland dysfunction, the tear surface becomes patchy, and the symptoms experienced are similar to those of dry eye. Obviously, the treatment for meibomian gland dysfunction differs from that of dry eye. Meibomian gland dysfunction needs to be confirmed by an eye specialist such as an optometrist or ophthalmologist. The eyelids can be examined with a slit lamp and the expression of oil with digital pressure to demonstrate the degree of clarity and function of the glands. Treatments



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CIMZIA (certolizumab pegol) in combination with MTX is indicated for:
- reducing signs and symptoms, including major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active RA.

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- the treatment of adult patients with moderate to severe PsO who are candidates for systemic therapy.

* Comparative clinical significance unknown.
CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; MRI: magnetic resonance imaging; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor alpha.

Consult the product monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information about:
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1. CIMZIA® Product Monograph. UCB Canada Inc. November 13, 2019.
2. Data on file. UCB, Inc.
3. Health Canada Notice of Compliance Database. Available at https://health-products.canada.ca/noc-ac/search-recherche.do;jsessionid=C19864F3D26560FC593BFC094A8B0CD1?lang=en. Accessed October 13, 2022.

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includes lid scrubs, hot soaks, and occasionally more advanced techniques such as 'Lipiflow'.[3]

For the patient who has an abnormal Schirmer's test result, the threat to the ocular surface is significant and can result in filamentary keratitis or punctate corneal ulceration. Initial treatment should of course include the use of artificial tears, by applying two drops in each eye on a regular basis, preferably four times a day. If artificial tears are used more than three to four times a day, then using preservative free preparations is preferable to prevent ocular irritation. Numerous artificial tear formulations are available, consisting of methylcellulose preparations, hyaluronate, polyethylene glycol, polyvinyl alcohol, glycerine and lacriserts. In fact, approximately 40 artificial tear preparations are available on the market.[4] There is no evidence for prioritizing these various formulations. Occasionally, dry eye is an issue during the night as well. Gel preparations can be helpful for these patients.

Some medical treatments for dry eye have been shown to provide benefit. For example, cyclosporin emulsion preparation can be applied topically. In a double-blind placebo controlled clinical trial,[5] treatment with cyclosporin emulsion provided benefit at a 0.05% concentration, administered as one drop in each eye twice daily. Cyclosporin emulsion preparation has been shown to improve the Ocular Staining Score at 3 and 6 months compared to placebo.[5] Another preparation, lifitegrast, a lymphocyte function associated antigen-1 (LFA-1) antagonist was also shown to provide benefit with significant improvement of fluorescein staining of the cornea at 84 days when compared with placebo.[6] This lymphocyte integrin inhibitor prevents T-cells from attaching to adhesion molecules on the cornea and inducing inflammation.

Varenicline, a smoking cessation tablet, was recently approved by the FDA in the United States in October 2021 as an aqueous nasal spray for treating dry eye. Varenicline is a highly selective nicotinic acetylcholine receptor agonist that binds with high affinity and selectivity at sites present on the trigeminal nerve within the nasal cavity. These receptors can mediate afferent signals in response to nasal stimuli, therefore, stimulating the lacrimal functional unit and producing tears. A 4-week trial that included 758 patients with dry eye has shown that treatment with varenicline demonstrated a significant improvement in the Schirmer's test result of 10 mm in the treatment groups ($p<0.0001$).[7] These participants had dry eye, and among them, a minority had Sjogren's syndrome. Minor side effects included sneezing immediately after the application of the spray, which was observed in 93.8% of the treatment groups.

If treatments such as artificial tears and topical medication are ineffective, more advanced topical measures can be considered. For instance, artificial tears can be created from the patient's own serum. To create the autologous serum tears, blood is drawn from the patient, spun down in a centrifuge to separate the blood components, then the serum is extracted from the sample and mixed with a preservative. The serum is then divided into aliquots and stored in a freezer at the patient's home. However, the vial of serum that is in use is stored in the refrigerator. A clinical trial has shown this treatment to be quite effective.[8] Platelet rich plasma is a variant of autologous serum tears, and is gaining recognition as an advanced treatment for patients with severe dry eye.[9]

> ***When artificial tears are insufficient to manage dry eye symptoms, other strategies can be considered.***

When artificial tears are insufficient to manage dry eye symptoms, other strategies can be considered. For example, punctal plugs can be inserted. Usually, punctal plugs are inserted into the lower eyelids alone, although in severe cases, plugs are inserted into the upper lid puncta as well. It is important that these devices be sized correctly by an eye specialist who has some experience inserting them. If the plugs are too small, they may fall out, and if they are too large, they may cause local irritation. Alternatively, the puncta can be cauterized, however, these orifices often re-cannulate.

Other treatment strategies exist. Enclosed spectacles can prevent tear evaporation and are practical and well tolerated for managing dry eye symptoms. These can be very efficient in alleviating symptoms for patients who want to read, work on a computer, or watch a video device. Inexpensive glasses to prevent tear evaporation include industrial working goggles or wrap around sunglasses. More attractive moisture guard spectacles can be purchased online and then taken to an oculist for the insertion of prescription lenses as indicated. Some eye specialists can provide these devices as well.

Scleral contact lenses are large ocular inserts with a purchase point on the sclera rather than the cornea. Lubricating liquid applied under these devices prior to insertion allows protection of the cornea and also provides a smooth refractory surface when filamentary keratitis or punctal erosion has caused corneal surface perturbation.

Treating Dry Mouth

Dry mouth can be more difficult to treat. Most patients are satisfied with sips of water. It is important to convey to the patient that a larger volume of liquid does not produce larger amounts of saliva. Indeed, over-consumption of liquid can result in nocturia and consequent disorganized sleep with resultant exhaustion. Sips of liquid should suffice. Gustatory stimulation is quite powerful in its ability to induce salivary flow. Sugar free candy or gum consumed throughout the day can be effective. In fact, any device in the mouth such as a button or cherry pit can induce the production of saliva. Lozenges are available that include adhesive that can be tacked onto the buccal surface of the patient's molar at bed-time, providing gustatory stimulation through the night.

There are many topical preparations that provide short-lived benefit to the sensation of oral dryness, but few give satisfaction greater than sips of water.

Salivary flow can sometimes be stimulated with parasympathomimetic preparations such as pilocarpine or cevimeline. In a 1999 double blind placebo-controlled trial, pilocarpine at 5 mg four times a day demonstrated a statistically significant improvement in unstimulated salivary flow at 12 weeks compared to a placebo.[10] Cevimeline is purportedly more specific for the salivary gland muscarinic 3 receptor with fewer patient complaints of sweating. A 12-week trial in which 197 patients with dry mouth received 30 mg of cevimeline three times a day demonstrated a significant improvement in the patients' assessment of global VAS compared to placebo.[11] However, the effectiveness of, and tolerance for, these preparations can be quite variable. Frequently reported complaints include sweating and urinary retention.

One must be aware of topical complications that arise from chronic oral dryness. Monilia overgrowth on the tongue, buccal membrane surfaces, and angles of the lips (angular cheilitis) can be managed with topical nystatin and/or ketoconazole. When monilia evolves to plaque formation or diffuse thrush, treatment with ketoconazole tablets at a dose of 200 mg daily for seven to ten days might be necessary. Often such overgrowth is recurrent, necessitating repeat courses of treatment as indicated.

Dental damage is another major issue associated with dry mouth. The pattern of decay observed with xerostomia is quite distinctive, with caries along the gingival margins, and pock-like fragmentation of the teeth. Incisors are ground down along the occlusive surface. The only conservative treatment with a modest proof of benefit is topical fluoride,[12] which can be applied locally on a regular basis in various forms, including the use of fluoride paint, fluoride gel trays worn for 30 minutes each night, or with a high fluoride concentration dentifrice used regularly. There is great concern over management with dental caps as decay frequently works its way into the root at the gum line. The success of dental implants in these patients depends on the status of the areolar ridge and the degree of gingival recession. A recent literature review assessed clinical outcomes of dental implants in patients with Sjogren's syndrome.[13] The review identified 19 studies for analysis totalling 712 implants placed in 186 patients; 705 implants were followed up for a mean of 72.5 months. The failure rate was 4.1% (29/705) at a mean time of 12.9 ± 31.7 months. The probability of failure was 2.8% (95% CI 1.6–4.1%). Hence, dental implants should be considered by dentists as a viable treatment option for patients with Sjogren's syndrome because the failure rate is fairly low. Patients may, however, experience a higher marginal bone loss around implants than patients from the general population. Intense regular maintenance (three times a year) with amalgam fillings in the molars and composite fillings along the gum line can ameliorate the rate of decay. Sterilization of the oral flora with chlorhexidine

rinse may be of benefit, however, this preparation does leave a brown stain on dental plaque.

Parotid Swelling

Parotid gland swelling is another complication reported frequently in patients with Sjogren's syndrome. This swelling can be painful and unsightly and is sometimes an indication of complications. Sjogren's syndrome begins with a ductal epithelial cell inflammation resulting in a highly deranged ductal drainage system, with areas of sialectasia and areas of ductal stenosis. The most common cause of intermittent parotid swelling is incomplete drainage of the salivary duct system. Once-daily massage of the gland can prevent gelification of pooled saliva with consequent plugging of the duct.

Glandular enlargement can occasionally be caused by infection. Such patients have fever, more severe pain, and more progressive symptoms. A parotid abscess may form. Management with antibiotics such as amoxicillin with clavulanic acid, clindamycin, or levofloxacin may be necessary. Abscess formation is rarely observed and requires surgical drainage.

The physician must always be aware that persistent swelling, new nodule formation, or evolution of regional lymph nodes can be possible signs of lymphoma. Such patients require thorough imaging as well as core or excisional tissue biopsy so that cells can be examined in situ with appropriate immune-peroxidase staining. Fine needle aspirate is usually inadequate for diagnosis.

Extraglandular Disease Management

Up to 40% of patients with Sjogren's syndrome experience extra glandular complications. These can include constitutional symptoms such as sweats, weight loss, lymphadenopathy, cutaneous vasculitis, peripheral neuropathy, interstitial pneumonitis, interstitial nephritis, and inflammatory arthritis. Such patients can be managed with traditional

Organ	Treatment standard	Later line treatment
Dry eyes	• Artificial tears and tear gel (methylcellulose) • Other eye drops (HydraSense, Systane, Hylo, Hylorunate, etc) • Anti-inflammatory drops (ex steroids) under direction of an ophthalmologist	• Cyclosporine eye drops (Restasis) • Lifitegrast (Xiidra) • Autologous serum • Surgery – blocking tear ducts • Pilocarpine, cevimeline • Occlusive glasses, contacs • Corneal graft
Dry mouth	• Water, water with sodium bicarb • More frequent dental care • Fluride trays • Biotene toothpaste • Sugar free candies • Moistir • Xylomelts	• Major dental work • Pilocarpine, cevimeline
Other Specific organ involvement (i.e. inflammatory arthritis, leukocytoclastic vasculitis, etc.)	• Hydroxychloroquine for specific indications • Azathioprine, Methotrexate, • Leflunomide • Glucocorticoids	• Biologics • Rituximab • Clinical trials • Possibly in future Dazodalibep

Table 2. Organ-specific treatment approach; courtesy of Arthur Bookman, MD; courtesy of Arthur A.M. Bookman, MD, FRCPC

immunosuppressants including corticosteroids, azathioprine, methotrexate, and mycophenolate.

Recently, a number of clinical trials have been conducted to evaluate the benefit from targeted biologic agents for the treatment of Sjogren's syndrome. A Novartis phase 2B double blind placebo-controlled trial examining the safety and preliminary efficacy of iscalimab,[14] an Fc silenced, fully human monoclonal CD40 antibody has recently concluded (TWINSS core study). Patients who received iscalimab demonstrated improvement in the European Sjogren's Syndrome Disease Activity Index (ESSDAI) score over 24 months. One secondary measure was unsimulated salivary flow, which also demonstrated improvement. There was also a trend toward an improved patient reported outcomes score European Sjogrens Syndrome Patient Reported Index (ESSPRI).

Novartis is currently engaged in another phase 3 trial of ianalumab, a monoclonal B-cell activating factor (BAFF) receptor antagonist which also depletes B-cells through antibody dependant cellular cytotoxicity. A phase 2B trial evaluating the safety and efficacy of ianalumab in patients with Sjogren's syndrome[15] has reported very promising results, showing a dose-related decrease in disease activity. Other agents are being evaluated in early-stage trials, including dazodalibep,[16] which is under development by Horizon Therapeutics. Dazodalibep is a CD40 ligand antagonist that blocks T cell interaction with CD40-expressing B cells, disrupting the overactivation of the CD40 ligand co-stimulatory pathway. A phase 2 study evaluating dazodalibep has demonstrated benefit and a phase 3 trial is underway.

Deucravacitinib (Bristol Myers Squibb) is a TYK2 inhibitor that leads to interferon inhibition. This drug has shown promising results.[17] Deucravacitinib has bypassed phase 2 studies in Sjogren's syndrome and has been launched into a phase 3 trial that is currently underway primarily in the United States.

The field for therapeutics of Sjogren's syndrome is finally making some progress. Rheumatologists need to be the coordinators for managing this condition that has such disparate manifestations. This requires developing familiarity in areas that do not usually fall into our realm of management, such as dental care, ocular complications, and salivary gland inflammation **(Table 2)**. Aside from developing a systematic approach to this disease, it is also helpful to engage a cadre of colleagues from other specialties who are open to communication and are interested in developing added expertise in managing Sjogren's syndrome.

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Updates in Treatment of Refractory Inflammatory Myositis

Kun Huang, MD, PhD, FRCPC, Aidan Pye, MD

Introduction

Idiopathic immune myopathies (IIM), also known as myositis, are a heterogeneous group of autoimmune diseases with varying phenotypes, prognoses, and treatment responses.[1] They are primarily characterized by muscle inflammation, however, many patients have extramuscular involvement including skin rash, arthritis, interstitial lung disease (ILD), cardiomyopathy, and gastrointestinal dysmotility. The discovery of myositis-specific autoantibodies (MSAs) has been a major advancement in the field of IIMs, shaping the new landscape of the clinical, phenotypical, histological, and serological correlations.[1] Based on this discovery, IIM can be more specifically classified into dermatomyositis (DM) (including amyopathic DM), antisynthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM), and overlap myositis (OM).[1] An increasing number of histological studies have revealed a misdiagnosis of PM because many patients who were previously diagnosed with PM were later reclassified to other forms of IIM, including IBM, IMNM, ASyS, or DM without a rash.[2]

Treatment of IIMs is challenging owing to their rarity, heterogeneity, and variable organ involvement, with most of the evidence for treatment coming from retrospective cohort studies. Only intravenous immunoglobulin (IVIg), rituximab, and exercise have evidence from randomized controlled studies to guide treatment decisions.[3,4] Consequently, no

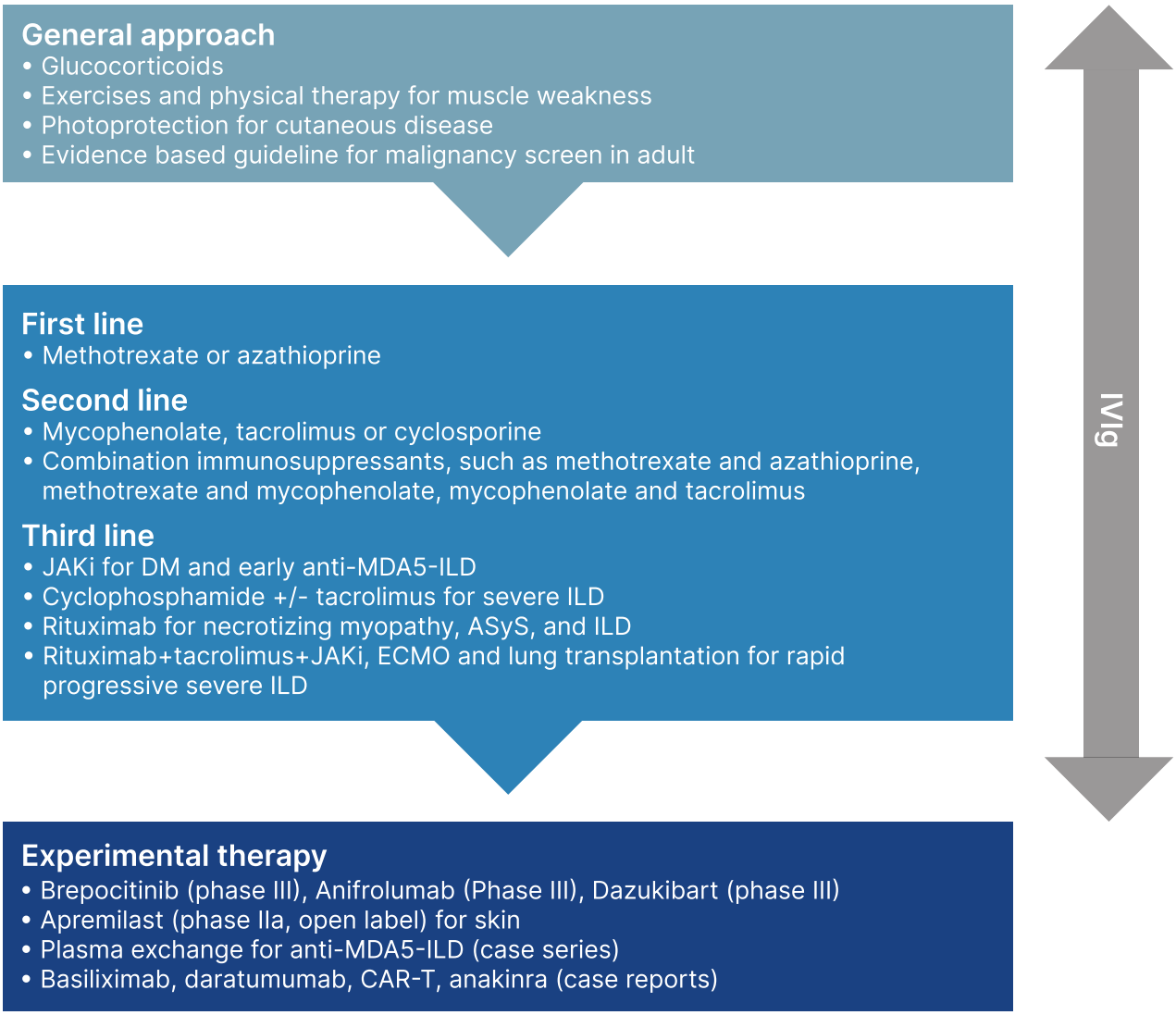

Figure 1. Common approach to IIM treatment (IBM excluded); courtesy of Kun Huang, MD, PhD, FRCPC and Aiden Pye, MD
Abbreviations: ASyS, antisynthetase syndrome; CAR-T, chimeric antigen receptor T cell therapy DM, dermatomyositis; ECMO: Extracorporeal Membrane Oxygenation; JAKi, Janus-kinase inhibitors; ILD, interstitial lung disease; MDA5-ILD, anti-melanoma differentiation-associated gene 5 dermatomyositis-interstitial lung disease

comprehensive consensus-driven guidelines exist for the treatment of IIMs.

The scope of this review is to summarize the general approach of myositis treatment with an emphasis on the management of refractory disease domains, including muscle, skin, and lung disease. As IBM does not respond to immunotherapy, and the mainstay treatment of IBM is exercise only, we will exclude IBM when referring to IIM or myositis in this review.

Current General Approach

The management of myositis includes non-pharmacological interventions, immunosuppressive therapies, and biologic agents, which are summarized in **Figure 1**. Adult-onset IIM is associated with an increased risk of cancer, particularly within the 3 years prior to and the 3 years after IIM onset. The International Myositis Assessment and Clinical Studies Group (IMACS) has recently developed an evidence - and consensus-based cancer screening guideline which stratifies cancer risk by age, myositis phenotypes, autoantibodies, and clinical features.[5]

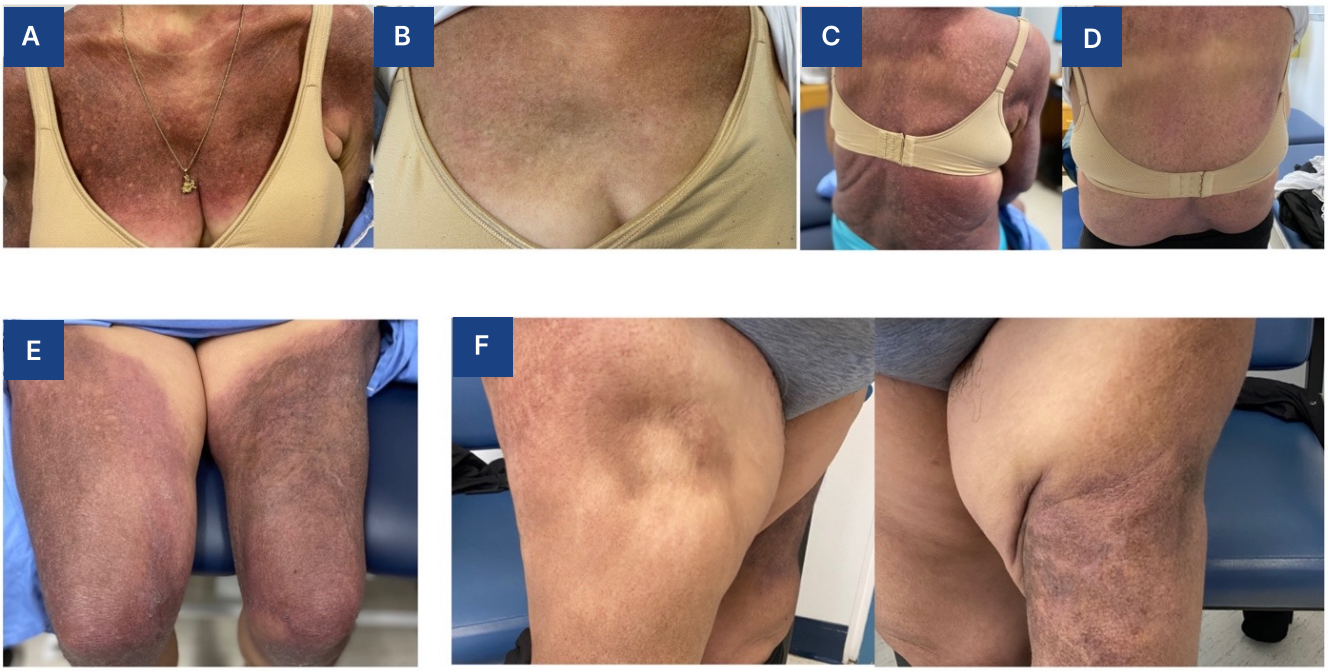

Figure 2. Improvement in cutaneous disease activity after a 2 month trial of tofacitinib
Photographs of a 64-year-old female with anti-SAE dermatomyositis for 6 years with severe myositis, dysphagia, widespread cutaneous rash, and subcutaneous panniculitis. Her myositis and dysphagia improved with high dose prednisone, IVIg, hydroxychloroquine, methotrexate, mycophenolate, cyclophosphamide, and rituximab; however, her cutaneous disease activity persisted . She was put on a trial regimen of tofacitinib 5 mg twice a day with IVIg. Pre-tofacitinib photographs are shown on panels **A, C** and **E**. After the 2 month trial regimen of tofacitinib, a significant improvement can be observed and is demonstrated in panels **B, D,** and **F**. Subcutaneous fat atrophy from panniculitis is also evident in panel **F**. Consent for the publication of the photographs was obtained from the patient; courtesy of Kun Huang, MD, PhD, FRCPC and Aidan Pye, MD
Abbreviations: IVIg, intravenous immunoglobulin; SAE, anti-small ubiquitin-like modifier activating enzyme

While many patients respond to first-line therapies and achieve a sustained remission, about 40% have relapsing/remitting or chronic refractory disease.[6] It is important to keep in mind that treatment for refractory cutaneous, muscular, and pulmonary diseases each follow a different treatment algorithm.

Refractory cutaneous disease

Most patients with cutaneous DM require systemic immunosuppression beyond antimalarials such as hydroxychloroquine.[7] Once a patient has failed to respond or has had a relapse of symptoms while taking steroid-sparing agents such as methotrexate with or without hydroxychloroquine, they are considered to have refractory disease. When assessing patients with persistent cutaneous disease, clinicians must review patients' compliance with strict photoprotection on a year-round basis, including the winter months. Daily use of broad-spectrum sunscreen (with a sun protective factor of at least 50), sun avoidance, wide-brimmed hats, and sun-protective clothing are strongly encouraged.[8]

If the area of affected skin is limited, further optimization with additional topical glucocorticoid and calcineurin inhibitors (CNIs), such as tacrolimus and pimecrolimus is reasonable.[8] Topical CNIs can be used on areas with thinner skin without the risk of atrophy.

However, refractory or severe cutaneous DM rash commonly requires an escalation of systemic treatment. Mycophenolate mofetil was shown to be an effective and well-tolerated agent for refractory cutaneous disease in case series and uncontrolled studies.[9] Typically, a higher dose of mycophenolate at 3 g daily is needed for clinical remission in cutaneous disease.[9] Furthermore, evidence suggests that Janus kinase (JAK) inhibitors are a viable treatment option for DM, especially in patients with refractory cutaneous DM[10,11] and calcinosis.[12,13] The most common choice of JAK inhibitor is tofacitinib at a dose of 5 mg or 10 mg twice a day. **Figure 2** illustrates an example of a dramatic cutaneous improvement after 2 months of tofacitinib at a dose of 5 mg twice a day in a 64-year-old female with anti-SAE DM who had previously failed therapy that included high-dose prednisone, IVIg, hydroxychloroquine,

methotrexate, mycophenolate, cyclophosphamide, and rituximab.

IVIg at a dose of 2 g/kg every 4 weeks is frequently used as a second-line or third-line treatment in combination with other immunosuppressive drugs. The efficacy of IVIg in cutaneous DM has been demonstrated in the large prospective randomized ProDERM study that included patients with the most severe skin manifestations.[14]

Calcinosis cutis is a particularly difficult skin manifestation to treat, and to date, there are no widely agreed upon effective pharmacotherapies. The consensus for treating ongoing cutaneous disease is to use immunosuppressants, while the addition of diltiazem (60-240 mg/day),[15] bisphosphonates (commonly pamindronate infusion at 1 mg/kg/day, for 3 days every 3 months),[16] and intravenous or intralesional sodium thiosulfate may be useful treatment options.[17] In many cases, surgical excision is the only treatment option.

Currently, there is conflicting evidence for the use of rituximab in cutaneous DM.[18,19] Therefore, rituximab is not primarily used for refractory skin disease; rather, it is reserved for refractory muscle and lung diseases. Other systemic treatment options for cutaneous disease, including tacrolimus, sirolimus, cyclophosphamide, azathioprine, dapsone, and cyclosporine have shown evidence that is limited to case studies and case series.

Refractory Muscle Disease

When treating refractory muscle disease, it is important to consider whether you have the correct diagnosis and if you have correctly discriminated between active disease, chronic disease damage, and deconditioning by further laboratory, imaging and electromyographic investigations.

For all IIM patients with muscle involvement, early initiation of physiotherapist-guided exercise regimens at the time of diagnosis should be considered as a standard adjunct intervention. Exercise programs are effective, well tolerated, and improve quality of life and muscle function.[20]

In general, myositis typically responds to treatment with glucocorticoids and traditional immunosuppressants. However, scleromyositis (OM) has a specific disease phenotype that includes a dropped head/bent spine due to neck and spine extensor muscle weakness; this phenotype is less likely to respond to immunosuppressants, and is associated with more severe myopathy and higher mortality.[21] Patients with dropped head often require neck collars for support.

When treating "PM" that is refractory to first-line therapies, start by revisiting the differential for an IIM, and ask whether this could be a PM mimic. Common conditions can mimic PM and could include PM with mitochondrial pathology (PM-mito), IBM, muscular dystrophy, or myositis related to drugs, infection, or cancer.

PM-mito is a rare and controversial form of inflammatory myopathy that shares many clinical and pathological features with IBM. The main pathological feature on muscle biopsy of PM-mito is endomysial inflammation with focal invasion of intact muscle fibres, and severe mitochondrial pathology; however, it lacks the characteristic rimmed vacuoles of IBM.[22] Similar to IBM, patients with PM-mito respond poorly to glucocorticoids. It is believed that PM-mito and IBM belong to a clinical continuum. One study has shown that a majority of patients with PM-mito had later developed clinically defined IBM.[22] In another study, 44% of patients who were initially diagnosed with PM-mito showed vacuoles typical of IBM on a repeat muscle biopsy.[23] We recommend that clinicians review the muscle biopsy with specialized muscle pathologists, keeping in mind that a repeat muscle biopsy may be warranted for diagnostic clarification. There is currently no pharmacologic cure for IBM. Current treatment strategies revolve around implementing supportive measures to address symptoms such as dysphagia, respiratory compromise, muscle weakness, and declining mobility.[24]

It is also important to distinguish the difference between disease activity (treatable inflammatory manifestations of the disease), disease damage (untreatable changes due to fatty replacement), muscle atrophy, steroid myopathy, and other comorbidities. Clinically, this may be challenging because muscle strength and functioning are not reliable methods of distinguishing active disease and damage. The most widely used laboratory measure is serum creatine kinase (CK), which unfortunately does not always correlate with disease activity. In fact, low or normal CK levels are well recognized in patients with active amyopathic DM. Conversely, persistent asymptomatic hyperCKemia in patients with treated IMNM is frequently observed despite normal muscle strength, magnetic resonance

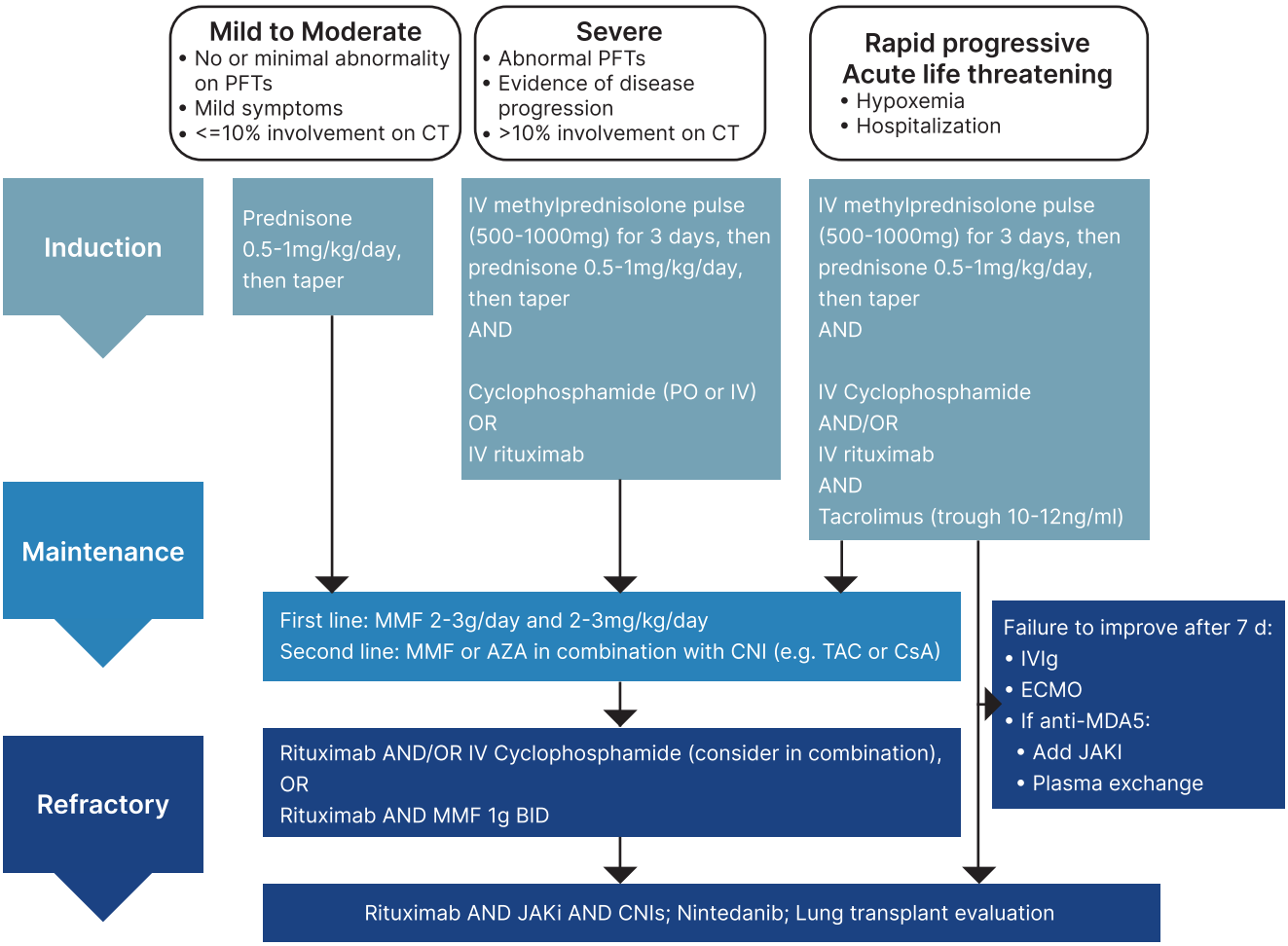

Figure 3. Diagram showing the treatment approach for myositis-associated interstitial lung disease; courtesy of Kun Huang, MD, PhD, FRCPC and Aidan Pye, MD

Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitors; CsA, cyclosporin A; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; IV, intravenous; IVIG, intravenous immunoglobulin; MDA5, anti-melanoma differentiation-associated gene 5 dermatomyositis; MMF, mycophenolate mofetil; PFTs, pulmonary function tests; PO, by mouth; TAC, tacrolimus

imaging (MRI), and electromyography (EMG). We recommend using MRI scans of the affected muscle groups to look for muscle edema suggesting active disease, or atrophy and fatty replacement suggesting chronic damage. Similar to MRI, EMG is useful in differentiating active myopathic processes from muscle atrophy and steroid myopathy. We do not routinely recommend repeat muscle biopsy to assess disease activity unless the underlying diagnosis is in question.

Refractory and Rapid Progressive ILD

ILD is a main driver of mortality and morbidity in IIMs, with a reported prevalence reaching 42.6%.[25] By far, the MSAs with the greatest pulmonary implications include anti-synthetase and anti-MDA5 autoantibodies. Anti-polymyositis-Scl (PM/Scl) and anti-Ku are two myositis-associated autoantibodies (MAAs) frequently associated with ILD, and are usually found in patients with OM.[26] Anti-Ro52/Tripartite motif containing-21 (TRIM21) is an MAA that is linked to more aggressive pulmonary and extrapulmonary disease in IIM.[27] The initial treatment should be determined by considering the severity of ILD (e.g., clinical symptoms, pulmonary functions, and chest high-resolution computed tomography findings) and poor prognostic factors (e.g. acute/subacute form, rapidly progressive ILD, anti-MDA5, older age, hypoxia, elevated ferritin, elevated C-reactive protein, and low forced vital capacity).[27]

In **Figure 3**, we outline the proposed treatment algorithm for myositis-associated ILD that is widely accepted by myositis and ILD experts and has been recently endorsed by the

2023 American College of Rheumatology (ACR) guidelines in Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease.[28] At our centre, this treatment algorithm is modified for some subgroups of myositis. In the setting of scleromyositis associated with stable ILD, there is no data to support starting high-dose glucocorticoid therapy for induction treatment. The benefits of glucocorticoids should be balanced with the potential side effects, as glucocorticoids have been associated with an increased risk of scleroderma renal crisis in systemic sclerosis. For stable usual interstitial pneumonia (UIP)-ILD without active extrapulmonary manifestations, the use of glucocorticoids may not be necessary. In both situations, initiation of steroid-sparing immunosuppressants alone without concurrent glucocorticoid therapy may be sufficient.

Outlook and Future Therapies

There have been tremendous advances in understanding the clinical, serological, and pathological phenotypes of IIM in the past decade; however, therapeutic interventions still lag behind those for other systemic autoimmune diseases. Traditional immunosuppressants have broad effects on the immune system, hence they often lead to frequent adverse effects. The need for new targeted therapies is urgent.

Results from clinical trials of targeted biologics such as tocilizumab (phase 2B), abatacept (phase 3), and ustekinumab (phase 3) have been disappointing[29,30]. Rituximab has been widely used in the treatment of refractory myositis including juvenile DM, IMNM, ASyS, and subtypes with ILD. The discovery of marked upregulation of Type I interferon-induced genes in DM has led to identification of new therapeutic targets. Type I IFNs and their downstream pathways can be targeted pharmacologically in several manners. One approach is to use monoclonal antibodies against IFNs (IFNB, such as with Darzukibart) or the IFN-receptors (IFNARs, such as with anifrolumab). Both Darzukibart and anifrolumab are undergoing phase 3 clinical trials for IIM. Another approach is to target the downstream signaling pathway of type I IFNs which lead to a wide usage of JAK inhibitors in the treatment of refractory DM including ruxolitinib, baricitinib, tofacitinib and upadacitinib.[10,11,31] Cytokines such as interleukin (IL)-4, IL-6, and IL-10 are significantly elevated in patients with myositis-associated ILD. These cytokines are mediated by JAK1, JAK3 and TYK2, which may be the basis for the use of tofacitinib in the treatment of anti-MDA5 DM patients with progressive ILD.[32] Clinical trials for the treatment of DM, including a phase 3 study of brepocitinib (a dual JAK1 and TYK2 inhibitor) and a phase 2 study of GLPG3667 (a TYK2 inhibitor) are currently underway.

Although rituximab, which targets CD20+ autoreactive naïve and memory B-cells, has been widely used in the treatment of refractory myositis, it has limited therapeutic efficacy in connective tissue disease and a delayed onset of action due to the persistence of autoreactive B cells in lymphatic organs and inflamed tissues.[33] In addition, long-lived plasma cells (CD20-, CD38+) can continue to circulate and secrete pathogenetic autoantibodies, resulting in refractory disease activity for months after initiation of rituximab. In our clinical experience, we commonly observe a delayed benefit of rituximab of several months after the first course, and occasionally observe a benefit only after the second course of rituximab. Daratumumab, an anti-CD38 human monoclonal antibody that depletes plasma cells, has recently been successful in cases of refractory lupus,[34] anti-SRP + IMNM,[35] anti-MDA5 DM ILD,[36] as well as other antibody mediated autoimmune diseases.[37] The addition of daratumumab to conventional immunosuppressants and rituximab may represent a new treatment paradigm for selected refractory and critically ill myositis patients.

Over the past two years, anti-CD19 chimeric antigen receptor (CAR) T cell therapy has gained traction in the treatment of refractory lupus, and there is evidence to suggest that it may be useful in the treatment of systemic sclerosis and myositis associated with ASyS.[38] Three case reports published in 2023 have shown the feasibility, tolerability, and efficacy of CAR T-cell therapy for the treatment of ASyS.[39-41] Remarkably, all three patients had failed rituximab, and one had failed both rituximab and ocrelizumab, both of which are anti-CD20 monoclonal antibodies. All three patients treated with CD19 CAR-T cell therapy had achieved a sustained drug-free remission.

The landscape of possible mechanisms now being explored to treat myositis has expanded remarkably in the past few years. Looking into the future of targeted myositis treatment, we are optimistic that 2024 will be an exciting year with several new therapies on the horizon. Planned clinical trials are expected to shed further light on the efficacy and safety of these promising therapies.

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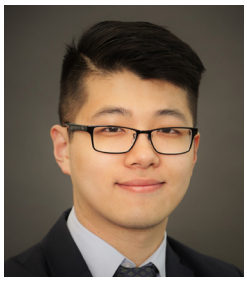

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What the Rheumatologist Needs to Know about IBD Treatment

Christopher Ma, MD, MPH, FRCPC

The Intersection of Immune-mediated Inflammatory Diseases

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), affect almost 1% of the Canadian population and are characterized by debilitating gastrointestinal (GI) symptoms including chronic diarrhea, rectal bleeding and abdominal pain.[1] Beyond involvement of the GI tract, up to half of patients with IBD will also experience extraintestinal manifestations (EIMs) or be diagnosed with comorbid immune-mediated inflammatory diseases (IMIDs), which are associated with substantial morbidity and impaired quality of life.[2,3] The most common of these are inflammatory joint diseases, including peripheral and axial spondyloarthritis or concomitant rheumatoid (RA) or psoriatic arthritis (PsA), affecting up to 1 in 5 patients with IBD.[4,5]

Inflammatory joint and bowel diseases share many pathophysiological similarities: both the joints and the gut mucosa represent the interface required to maintain tissue homeostasis and are under constant exposure to mechanical, microbial and chemical forces.[6,7] The pathogenesis of inflammatory arthritis and IBD are both characterized by genetic susceptibility with shared risk loci, triggered by environmental exposures that result in aberrant immune activation with complex downstream cytokine and regulatory cell signaling, culminating in progressive end-organ joint or gut damage. Given these similarities, there has been a recent emphasis on classifying IMIDs not based on anatomical organ involvement, but rather, by shared signature molecular cytokine hubs, which better characterize the mechanistic underpinnings of these conditions.[8]

Over the past 20 years, tremendous progress has been made in the medical management of moderate-to-severe IBD. In 2024, multiple classes of both monoclonal biologic therapies as well as novel small molecule immunosuppressants have been approved for the treatment of CD and UC. This includes biologics targeting common effector pathways and inflammatory cytokines such as tumor necrosis factor (TNF)-α, Janus kinases (JAKs) and interleukin (IL)-23.[9] Notably, many, if not most, of the therapeutic options and treatment strategies that have shaped IBD care have been "borrowed" from rheumatology. For example,

promising molecular targets generally have demonstrated efficacy in inflammatory skin or joint diseases before clinical development for CD or UC. Many therapeutic strategies in rheumatology have been adopted in IBD, including a "treat-to-target" approach which is now the standard of care in 2024.[10] This concept of optimizing or changing therapy for patients who have not achieved their therapeutic goals was pioneered by rheumatologists and was only recently adopted by gastroenterologists.

Recognizing the growing therapeutic armamentarium that may have efficacy for joint, skin and gut manifestations, this review will summarize the state-of-the-art evidence supporting medical therapies for this complex patient population and provide practical considerations for these often difficult treatment decisions. Surgical treatment decisions will not be reviewed here, recognizing that although surgery plays an important role in managing IBD, its place in managing other immune-mediated inflammatory disorders is limited.

Tumor Necrosis Factor Antagonists: Do they Still Play a Role?

TNFα is a common downstream effector pathway for many IMIDs and was the first advanced therapeutic target approved for the treatment of moderate-to-severely active CD and UC.[11,12] Inhibiting this master cytokine has proved to be highly effective in almost all major forms of inflammatory arthritis. For gastroenterologists, TNF antagonism was the only advanced mechanism of action available until the mid-2010s and accordingly, there was substantial interest in understanding how TNF antagonists could be optimized for IBD care. Several observations are worth noting. First, TNF antagonists remain the preferred first-line treatment option for many forms of IBD. Despite an increasing armamentarium of therapeutic options, infliximab remains the only therapy with robust data to support its use as a rescue agent in acute, severe UC and has been demonstrated to reduce the short-term likelihood of colectomy among hospitalized patients.[13] Infliximab is also the only molecule currently with randomized controlled trial (RCT)-level evidence to support its use in perianal fistulizing CD.[14,15] Second, the immunogenicity of TNF antagonists remains a clinical challenge. In the United Kingdom PANTS study, 62.8% of infliximab-treated and 28.5% of adalimumab-treated patients developed anti-drug antibodies.[16] To ameliorate this risk, the combination of infliximab and azathioprine has been demonstrated to improve clinical, corticosteroid-free and endoscopic remission in CD and UC, compared to infliximab monotherapy.[17,18] Third, there has been substantial investigation evaluating whether monitoring of serum anti-TNF concentrations can be used to improve treatment outcomes.[19] To date, monitoring drug levels and proactively adjusting treatment dosing based on these drug concentrations has not proven more effective in adult patients with IBD. However, reactive testing of therapeutic drug monitoring in patients who lose response can help delineate mechanisms of drug failure and guide future decision-making.[20]

Given their efficacy in both joint and gut diseases, as well as a long track record of clinical efficacy and safety, should TNF antagonists remain the "go-to" therapy for patients with IBD and concomitant IMIDs? TNF antagonists have flexibility in the route of administration and dosing, as well as broad anti-inflammatory effects and consequently, dynamic efficacy across many different phenotypes of IBD, as well as for several IMIDs, including ocular, dermatologic and rheumatologic indications. However, several drawbacks should also be considered. First, TNF antagonists may not be the most effective treatment for some patients with IBD: for example, vedolizumab is superior to adalimumab for achieving clinical, endoscopic and histologic outcomes in UC.[21] Second, TNF antagonists have been associated with an increased risk of serious infections and some malignancies, including melanoma.[22,23] Third, the optimal strategy for using TNF antagonists involves concomitant immunosuppression with azathioprine or methotrexate, which may be beneficial for joint-related EIMs but also increase the risk profile of therapy, particularly for older adults.[24] Fourth, TNF antagonist dosing in IBD is generally higher than for rheumatologic indications, and not all TNF antagonists used for rheumatologic diseases are effective for IBD: for example, golimumab is not approved in CD, etanercept is not effective in either CD or UC, and certolizumab is not approved for IBD management in Canada. Therefore, although TNF antagonists remain a principal therapeutic option in patients with EIMs or IMIDs, other treatment options that are effective across multiple disease states also warrant consideration **(Table 1)**.

Mechanism of Action	Treatment Options	IBD Approvals	Approved for other IMIDs
TNF antagonists	Infliximab Adalimumab Golimumab	CD/UC CD/UC UC	Yes
Anti-integrin	Vedolizumab	CD/UC	No
Anti-IL12/23p40	Ustekinumab	CD/UC	Yes
Anti-IL23p19	Risankizumab Mirikizumab	CD UC	Yes
Janus kinase inhibitors	Tofacitinib Upadacitinib	UC CD/UC	Yes
S1P receptor modulators	Ozanimod Etrasimod	UC UC	No

Table 1. Therapeutic options approved for the treatment of IBD in Canada; courtesy of Christopher Ma, MD, MPH, FRCPC
Abbreviations: CD Crohn's disease; IL interleukin; IMID immune mediated inflammatory disease; S1P sphingosine 1 phosphate; TNF tumor necrosis factor; UC ulcerative colitis

JAK Inhibitors: Potent Immunosuppression but at What Cost?

In 2018, tofacitinib was approved in Canada for the treatment of moderate-to-severe UC.[25] This marked an important moment in the landscape of IBD therapeutics, representing the first non-biologic, oral advanced therapy available for treatment. In the past two years, upadacitinib, a reversible JAK-1 selective inhibitor, has also been approved for both UC and CD, with 8-12 weeks of high-dose induction dosing (45 mg daily) and then with maintenance dosing with either 15 mg or 30 mg daily.[26,27] Upadacitinib is currently the only oral advanced therapy that has demonstrated efficacy in CD; tofacitinib is not approved in CD.

Overall, the efficacy profile of JAK inhibitors offers substantial promise for IBD care. Although no direct treatment comparisons are available, multiple network meta-analyses have found that upadacitinib is likely to be the single most efficacious therapy for achieving clinical and endoscopic remission in patients with moderate-to-severely active UC.[28-30] In the registrational trial program, upadacitinib was demonstrated to be superior to placebo for inducing and maintaining clinical, endoscopic and histologic endpoints at Weeks 8 and 52, and importantly, this was observed in both patients naïve to other advanced therapies and in highly refractory patients who had failed multiple prior biologics.[26] Early treatment response was observed: statistically significant improvements in patient-reported outcomes compared to placebo were observed even within 24 hours of treatment.[31,32]

In two Phase 3 induction trials (U-EXCEL and U-EXCEED), participants with moderate-to-severe CD treated with upadacitinib 45 mg daily for 12 weeks were more likely to achieve clinical remission and endoscopic response (defined by at least a 50% reduction in endoscopic disease severity).[27] These induction trials were also the first IBD trials to require mandatory corticosteroid tapering during induction, and a significantly greater proportion of patients treated with upadacitinib achieved corticosteroid-free remission at Week 12 and Week 52 compared to placebo. A post-hoc analysis suggests that upadacitinib is effective for reducing the burden of perianal fistulizing CD, and in patients with active baseline EIMs, treatment with upadacitinib has been demonstrated to

reduce the proportion of patients with active joint symptoms (43.5%-54.8% among patients receiving upadacitinib compared to 20.0% of patients receiving placebo at Week 52).[33,34]
Beyond the efficacy signal, the other advantages of oral advanced therapy in CD should be highlighted. These agents can be initiated quickly without the need for concomitant corticosteroid induction; maintenance dosing is flexible (15 mg and 30 mg for upadacitinib); there is no risk of immunogenicity; the short half-life is favourable for holding treatment if required; and upadacitinib is effective across multiple IMIDs, including RA, PsA, axial spondyloarthritis, and atopic dermatitis.[35]

The broad efficacy signal in IBD has been somewhat tempered by concerns about the safety of this class of treatment. In patients with RA over age 50 with established cardiovascular risk factors, the ORAL Surveillance trial emphasized the potential risks of tofacitinib concerning major adverse cardiovascular events (MACE), malignancy, venous thromboembolism (VTE), herpes zoster (HZ), and other serious and opportunistic infections.[36] Whether these concerns are generalizable to patients with IBD is less clear. For example, in over 9.5 years of follow-up data from the tofacitinib UC trials, a similar signal for VTE or malignancy has not been demonstrated.[37] While the signal for HZ was observed in IBD trials of tofacitinib, filgotinib (not licensed in Canada), and upadacitinib, <5% of trial participants were vaccinated, and observational Canadian data suggests that the risk of HZ is much lower in real-world experiences where >80% of patients have received HZ vaccination before induction therapy.[38] JAK inhibitor safety has now undergone formal regulatory review with multiple agencies, including the US FDA, the European Medicines Agency and Health Canada. While there are risks associated with this class of treatment, they remain an especially potent therapeutic option in IBD, particularly for patients with severe or extensive disease and those with prior biologic treatment failure.

Targeting IL23p19: Superior to IL12/23p40?

There has been substantial investment in the development of IL23p19-specific antagonists for treatment of IBD, given observations that p19 inhibition was significantly better than IL12/23p40 blockade in patients with psoriasis.[39] The past two years have seen the approvals of two p19 antagonists, risankizumab and mirikizumab for moderate-to-severe CD and UC, respectively.[40-42]

Do these agents represent a significant advance compared to previously available therapies for IBD? In CD, the efficacy and safety of risankizumab was demonstrated in the Phase 3 ADVANCE, MOTIVATE and FORTIFY trials.[40,41] These were the first RCTs in CD to measure endoscopic response as a coprimary endpoint, both after induction at Week 12 and among induction responders at Week 52. The proportion of participants who achieved and sustained endoscopic response was significantly higher than that of participants receiving placebo, and this observation was confirmed in both treatment-naïve and treatment-experienced patients. For many gastroenterologists, the more relevant clinical question was whether risankizumab would be superior to ustekinumab, an established IL12/23p40 antagonist that has proven efficacy in both CD and UC.[43,44] This question was evaluated in the Phase 3 SEQUENCE trial, an open-label, head-to-head comparator trial in patients with moderate-to-severe CD, all of whom had failed a prior TNF antagonist.[45]
A total of 520 patients were randomized. At Week 24, 58.6% (75/128) of participants receiving risankizumab vs 39.5% (54/137) of participants receiving ustekinumab were in clinical remission. At Week 48, risankizumab demonstrated superiority over ustekinumab for achieving endoscopic remission (31.8% vs. 16.2%, P<0.001). Risankizumab was also superior to ustekinumab for achieving Week 48 clinical remission, steroid-free endoscopic and clinical remission, and Week 24 endoscopic response. Currently, two other IL23p19 antagonists (guselkumab, mirikizumab) are in late-stage clinical development for CD; both registrational trials have internal comparison arms to ustekinumab.

Results in UC with p19 antagonism are also significant, albeit less dramatically superior to existing treatment options when compared to CD. In the Phase 3 LUCENT trial, a significantly higher proportion of participants with moderate-to-severely active UC treated with mirikizumab achieved clinical remission (treatment difference 11.1%, P<0.001), clinical response (Δ21.4%, P<0.001), endoscopic remission (Δ15.4%, P<0.001), and histologic-endoscopic mucosal improvement (Δ13.4%, P<0.001).[42] Positive results for guselkumab and risankizumab in UC have also recently been reported.[46]

Antagonism of IL23p19 has several advantages. First, the safety profile of this class of therapy is supported across multiple indications. Second, these agents are highly effective for some IMIDs, particularly in psoriasis where this class of therapy induces and maintains complete skin clearance.[47] Both risankizumab and guselkumab have also been demonstrated to be effective for the treatment of psoriatic arthritis.[48,49] Third, these agents are effective in both CD and UC, and effectively achieve endoscopic endpoints that represent the long-term treatment target in IBD. However, it should also be considered that p19 antagonism is not an effective mechanism for patients with axial spondyloarthritis and is not approved for rheumatoid arthritis.[8]

Gut-selective Mechanisms in Patients with IMIDs

Vedolizumab is a gut-selective α4β7 integrin antagonist approved for the treatment of both moderate-to-severe CD and UC.[50,51] The unique mechanism of vedolizumab interrupts the trafficking of gut-targeted lymphocytes by blocking the interaction between integrin receptors and the mucosal addressin cell-adhesion molecule (MAdCAM)-1 on gut endothelium. This mechanism has specific advantages for the IBD population. First, targeting a critical component of IBD pathophysiology is associated with substantial efficacy, particularly in patients with early CD and UC. In a head-to-head clinical trial vedolizumab was shown to be more effective than adalimumab for inducing and maintaining clinical, endoscopic and histologic remission in UC.[21] Vedolizumab is also effective in subgroups of patients with IBD, including those with perianal CD and chronic antibiotic-resistant pouchitis.[52,53] This efficacy has been paired with a remarkable safety profile. Patients treated with vedolizumab are generally not considered to be systemically immunosuppressed because of the mechanism of action, and in long-term follow-up there has not been a signal for infection or malignancy.[54]

One obvious potential downside to the use of vedolizumab as a gut-selective therapy is that it may not be effective for patients with other IMIDs or EIMs. However, this is quite controversial. In a post-hoc analysis of the registrational GEMINI vedolizumab program, Feagan et al showed that vedolizumab was associated with a reduced likelihood of new or worsening joint symptoms in CD patients. This finding has been corroborated in several observational cohorts, where up to half of patients with IBD-related arthralgia experienced improvement with vedolizumab treatment.[55,56] It is hypothesized that this may relate to reduction in luminal inflammation with subsequent control of EIMs that are linked to active IBD.

Should vedolizumab be avoided in patients with EIMs? This is a challenging clinical scenario. Given its safety profile, vedolizumab remains an important therapeutic option in IBD, especially in elderly or comorbid patients. It is often a preferred treatment option for patients given that it can be administered subcutaneously or intravenously and is gut selective. While generally not a first-line choice for patients with concomitant EIMs, many patients may still choose vedolizumab in this setting and in these situations. It is worth evaluating both gut and joint activity after at least 3-6 months of treatment. In some cases, combination therapy with another immunosuppressant may be required if luminal control is achieved but there remain active IMIDs or EIMs. There has also been increasing interest in using combination treatment approaches, including dual biologic or advanced therapies.[57] These scenarios often use vedolizumab as an "anchoring" therapy given its favourable safety, although the long-term cost-effectiveness and sustainability of such a strategy requires further assessment.

Finally, two additional oral small molecule sphingosine-1-phosphate receptor modulators, ozanimod and etrasimod, have been approved for the treatment of UC.[58,59] These agents interrupt lymphocyte trafficking by blocking the egress of activated lymphocytes out of lymph nodes. Etrasimod is currently under development for the treatment of atopic dermatitis but its efficacy for other non-GI inflammatory manifestations is unclear.

Conclusion

The management of complex patients with IBD with concomitant IMIDs or EIMs requires thoughtful consideration of medical therapy, often in collaboration with multidisciplinary partners. The "right" choice of treatment should consider the patient and disease profile, individual patient preferences, and shared pathological mechanisms of disease. The subsequent monitoring of treatment response and treat-to-target approaches must also capture GI, rheumatologic and other end-organ targets. In the past several years, multiple novel classes of treatment have

been approved for IBD, many of which have broad-spectrum effects and can be effective for both IBD and other rheumatologic indications. However, the advantages and disadvantages of these new options should be balanced against the potential of existing therapies for treating patients with complex disease manifestations.

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Management of Rheumatologic Immune-Related Adverse Events (Rh-irAEs) – An Overview of Immunosuppressive Therapies

Shahin Jamal, MD, Jenny Li, MD, Marie Hudson, MD, Carrie Ye, MD

Introduction

Cancer treatment has entered a new era with the expanding role of immunotherapy, in particular immune checkpoint inhibitors (ICIs). ICIs, including those that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death protein-1 (PD-1), and programmed death ligand-1 (PD-L1), work by blocking the intrinsic down-regulators of the immune system, leading to sustained activation of effector T-cells to enhance endogenous anti-tumour immune responses.

The potential downside of sustained immune activation is the risk of breaking immune tolerance, which can lead to immune-related adverse events (irAE). These have been reported in up to 80% of patients who receive ICI monotherapy and in 95% of those who receive ICI combination therapy.[1] The most common irAEs include skin rashes, gastrointestinal inflammation, and endocrinopathies, but they can essentially involve any major organ in the body, and multiple organs simultaneously.[1,2] They can occur anytime during treatment and sometimes after cessation of immunotherapy. The severity can vary from mild to severe, sometimes requiring hospitalization, and even rarely leading to death. The severity of irAEs has traditionally been graded on a scale of 1 to 5 based on the Common Terminology Criteria for Adverse Events (CTCAE), which can also be used help determine appropriate management.[3-5] Grades 1 and 2 are considered mild, Grades 3 and 4 include severe adverse events, and Grade 5 toxicities are those that are fatal.[3] Management ranges from clinical monitoring, temporarily holding the ICI, symptomatic support, and the use of immunosuppressive agents, either short or long term.[1,2] While many irAEs are transient, others require chronic immunosuppression, and often lead to permanent discontinuation of ICI therapy.

Rheumatologic irAEs (Rh-irAEs) have increasingly been reported and include ICI-associated arthralgias (ICI-arthralgias), myalgias (ICI-myalgias), inflammatory arthritis (ICI-IA), PMR-like presentation (ICI-PMR), myositis (ICI-myositis), vasculitis (ICI-vasculitis), and sarcoid like reactions (ICI-SLR). Rheumatologists have a key role in the diagnosis and management of Rh-irAEs, in collaboration with the patient and their oncologist, and should aim to support the oncologist to maintain effective cancer care.[6]

While there are currently no large-scale clinical trials that provide a guide for the optimal management of Rh-irAEs, recommendations and guidelines are available from organizations such as the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Society for Immunotherapy of Cancer (SITC).[2,4,5] In general, CTCAE Grade 1 toxicities can often be managed conservatively, those that are classified as Grade 2 can be managed with non-steroidal anti-inflammatory therapies, intra-articular injections, and low dose prednisone, while Grade 3-4 toxicities often require more aggressive immunosuppressive therapy with the temporary or permanent discontinuation of immunotherapy.[7]

With the delicate balance of immune activation for enhancement of anti-tumour responses, and immune suppression for management of irAEs, there is a concern that high dose and long-term immunosuppression, may “undo” the anti-tumour response to ICIs. In this article, we will review the available evidence on efficacy and safety of corticosteroids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), and biologic disease modifying anti-rheumatic drugs (bDMARDs) in the management of Rh-irAEs.

Corticosteroids

Corticosteroids are the most commonly used immune-modulators across the majority of irAEs, including Rh-irAEs, and have been used intra-articularly, orally, and intravenously, at various doses, with good success. They are considered the standard of care first-line intervention in most cases.[5] Recommended starting doses should be guided by type and severity of irAE. Although the majority of irAE respond to systemic corticosteroids, there is a proportion that may be refractory or relapse with steroid taper.[8]

Oral prednisone has been effectively used across all Rh-irAEs, including ICI-associated IA, PMR, myositis, and SLR. A reasonable starting dose of prednisone is 10–20 mg daily for patients with mild-to-moderate symptoms and up to 1 mg/kg daily for those with severe symptoms, significantly impacting daily function or involving a major organ.[2,9] Intra-articular corticosteroid injection can be considered in cases of mono-or oligoarthritis, particularly involving large joints,[2,4,9] and high dose intravenous corticosteroids may be required for severe ICI-myositis, especially when respiratory muscles are affected.

As with corticosteroid use in general, corticosteroids for treatment of irAEs should be used for the shortest duration and at the lowest dose possible. Patients should be monitored for common side effects, including infections, mood changes, gastrointestinal intolerance, hyperglycemia, hypertension, and bone loss and treated with concomitant prophylaxis as indicated including gastrointestinal and bone protection.

The data on safety of steroids to treat irAEs is conflicting. In pre-clinical studies, even low dose steroids were shown to markedly alter the anti-tumour activity of T-cells.[10] In a pooled meta-analysis of retrospective studies, there was no significant impact of steroids used for the management of irAEs on progression free survival (PFS) or overall survival (OS).[11] However, visual inspection of the forest plots showed tremendous heterogeneity, with some studies suggesting harm and others indicating a benefit. Some of the inconsistencies in the existing data have been attributed to steroid dose, timing of steroid initiation, and type of irAE. In a retrospective study comparing prednisone dosing for the management of ICI-hypophysitis in melanoma patients, high dose prednisone (> 7.5 mg daily average) was associated with a lower OS.[12] In another retrospective analysis of over 500 melanoma patients treated with a PD1 inhibitor, those who experienced early onset irAEs (within 8 weeks) and were treated with high dose prednisone (> 60 mg/d) had a lower PFS and OS.[13] Finally, a recent study by Gente et al. observed strong trends toward worse PFS and OS at prednisone equivalent doses of > 10 mg, and this trend was even more pronounced at doses of > 1 mg/kg, in patients with Rh-irAEs, but not in patients with other irAEs.[14]

All of the currently available data on the safety of steroids is limited by confounding and bias. Other confounding factors include the underlying tumour type, duration of steroid exposure, and other underlying patient factors.[15] Until there are well designed randomized trials, corticosteroids should be used at the lowest effective dose and tapered as soon as possible to optimize tumour outcomes.

Conventional Synthetic Disease-modifying Antirheumatic Drugs

There are no prospective, randomized trials on the optimal use of systemic immunosuppression in patients with irAEs. CsDMARDs, including methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), azathioprine (AZA) and mycophenolate mofetil (MMF) have been successfully used in numerous case reports and case series of patients with a variety of irAEs, including Rh-irAEs.[1,16-18] In these limited studies, without control groups, there have been varying clinical responses and no apparent negative impact on ICI efficacy. Of 177 patients in the multicentre CanRIO cohort, the majority of whom had ICI-IA, 42 were treated with csDMARDs, including HCQ (62%), followed by MTX (40%).[19] Of those treated with HCQ and MTX, 65% and 82% respectively had a complete or partial response to their ICI-IA.

In a recent systematic review, Barron et al found that Rh-irAEs accounted for 20% of patients with chronic irAEs, of which ICI-IA was most common.[20] This is consistent with Canadian data which showed 83% had chronic inflammatory arthritis persisting for at least three months after stopping ICI therapy.[21] In the majority of cases, csDMARDs are reserved for patients with steroid-refractory, steroid-dependent or life-threatening presentations. In some instances, particularly in patients with mild symptoms, agents such as HCQ, MTX, and SSZ can be used instead of corticosteroids.

The choice of immunosuppression often mirrors the agents commonly used to treat idiopathic diseases with similar manifestations. For example, ICI-hepatitis and ICI-pneumonitis are often treated with MMF, while ICI-IA is often treated with MTX, HCQ, and SSZ, and ICI-myositis with AZA and MMF.[22,23] There are no large-scale clinical trials that comparatively demonstrate effectiveness of one csDMARD versus another in any given irAE. As such, treatment decisions are left to the rheumatologist, or other specialists involved. Other considerations when choosing an immunosuppressant agent include the severity of symptoms, overlapping comorbidities, expected tolerance, and patient preference.

While csDMARDs have been reported to be effective steroid sparing agents for treating Rh-irAEs, their impact on the efficacy of ICIs is unclear. Due to limited sample size in most studies, immunosuppressive drugs, including glucocorticoids, csDMARDs and bDMARDs, are often grouped together for examining outcomes related to immunosuppression. A recent cohort study of patients with advanced melanoma treated with ICIs showed that immunosuppressive drugs, including glucocorticoids, infliximab, and MTX, negatively impacted the efficacy of ICIs if started before the initiation of ICI therapy, but had no impact if started after ICI initiation.[24] Another cohort study observed that the use of glucocorticoids with and without other immunosuppressive agents was actually associated with a longer OS.[25] Clinical studies examining the isolated impact of csDMARDs on ICI efficacy are lacking. Mouse studies have found contradictory results with HCQ.[15] Nonetheless, clinical trials evaluating cancer treatment regimens that include combination csDMARDs with ICI are underway.[15] At this time, most evidence points to no definite negative impact of csDMARDs on ICI efficacy when started for irAE treatment.

Biologic and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs

Biologic and targeted synthetic DMARDs (tsDMARDS), including tumour necrosis factor alpha inhibitors (TNFi), interleukin 6 inhibitors (IL-6i) and Janus kinase inhibitors (JAKi) have become standard of care for many auto-immune diseases including inflammatory arthritis and colitis. They have been increasingly used to treat a variety of irAEs, particularly those that are refractory to other immunosuppression, and with life-threatening presentations. In certain cases, they are used in early disease, for short duration, in order to induce remission of irAE and minimize steroid exposure.

Infliximab, a TNFi, has been a cornerstone for the treatment of ICI-colitis, particularly in patients who flare with steroid taper, or require high doses of steroids to control inflammation. Preclinical studies suggest less negative effect on antitumour activity compared to corticosteroids.[10] TNFi have been used successfully in many case series and case reports of patients with ICI-IA, ICI-SLR, and ICI-myocarditis.[6]

Tocilizumab is a promising option for treating ICI-IA.[26] It has also been used for refractory ICI-myositis and ICI-myocarditis. Preclinical data suggest that blocking IL-6 may reduce immunotherapy toxicity and promote tumour immunity,[27] making it an ideal agent. However, clinical data is still lacking with most experience based on case reports or case series.

Similarly, there is increasing interest in the use of JAKi for refractory disease, including ICI-myocarditis and myositis.[28,29] The JAK/STAT signaling pathway may play a role in tumorigenesis and tumour evasion, and blocking this pathway could have a synergistic anti-tumour effect on ICI therapy. However, JAK/STAT signalling may be important for the upregulation of immune checkpoints (e.g. PD-L1), and some experts argue that JAK inhibition could potentially reduce the expression of ICI targets and interfere with the effectiveness of ICI therapy.[30,31] Further clinical experience is needed to define the role of JAKi for the treatment of irAE.

Finally, there is limited experience with other biologic agents such as IL-17 inhibitors (e.g. secukinumab), T cell modulators (e.g. abatacept, alemtuzumab), and rituximab, all of which have been used in refractory and life-threatening cases, however, due to their mechanism of action, they are not considered first-line agents of choice.[6]

As with csDMARDs, there are no well-designed prospective clinical trials that compare the use of b/tsDMARDs with the standard of care or that comparatively demonstrate the effectiveness of one b/tsDMARD versus another for treating any given irAE. The data on the impact of b/tsDMARD use and tumour outcomes is mixed, and predominantly includes patients who have received TNFi used to treat ICI-colitis. In colitis, doses of TNFi are usually given for short duration (1–3 months), whereas ICI-IA may require longer duration of treatment, the impact of which is not

yet known. In a recently published retrospective multicentre observational study of patients with ICI-IA treated with either MTX, TNFi or IL-6i, those treated with a bDMARD experienced more rapid arthritis control, but also had a shorter time to cancer progression.[26] At present, given the lack of definitive safety evidence, we recommend use of b/tsDMARDs only in csDMARD-refractory cases or for the induction of remission, and for as short a duration as tolerated.

Conclusion

With the increasing use of ICIs for cancer, rheumatologists and other specialists will increasingly be relied upon to help guide management of the resulting auto-immune toxicities. Much of what we do now has been guided by clinical experience, case reports, and case series, and extrapolated from idiopathic diseases that manifest with similar phenotypes. We urgently need well-designed, prospective clinical trials to guide treatment decisions. In the interim, early consultation and strong collaboration is needed between rheumatologists, oncologists, patients, and other health care providers to optimize patient outcomes. It is important for us all to remain current with the changing landscape of data emerging in this field.

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