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Biologics in DERMATOLOGY

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- Benefit and risk considerations in anti-TNF therapy
- Treatment of cutaneous vasculitis

Focus on: Anti-TNF therapy — Counselling your patients

Patients with moderate-severe psoriasis are often underserved by our traditional approach to treatment; surveys suggest that the majority want their disease treated more aggressively.[1] Recognition of the significant quality of life issues faced by psoriasis patients and the availability of highly effective anti-TNF therapies is contributing to an ongoing shift in approach to psoriasis treatment. Complete clearance of the skin has become an attainable goal since the introduction of biologics.

Many experts, including those who helped develop the 2009 Guidelines, believe there is no clinical reason to delay use of biologics in moderate-severe psoriasis,[2] although [patients'] cost remains an important consideration. Continued monitoring of long-term safety along with effective patient counselling will help guide optimal use of TNF-blockers in psoriasis.

Patient-centred psoriasis care

The 2009 *Canadian Guidelines for the Management of Plaque Psoriasis* revolve around the concept of patient-centred psoriasis therapy. Given the very high (40-70%) rates of non-adherence to psoriasis treatment,[3,4] "find a therapy my patient will work with" has become the new guideline mantra.[2]

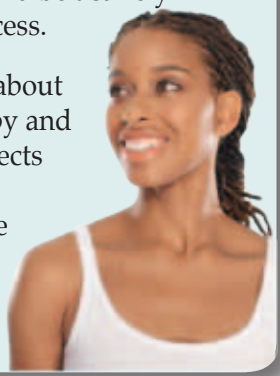
Choice of management strategies should take into consideration disease severity and its impact on daily function and quality of life (QoL) relative to a therapy's potential benefits, side effects, cost and convenience, with the goal of enhancing health related quality of life (HRQL) and subsequent adherence to treatment. Engaging the patient in treatment selection may help to manage expectations and ensure that the selected treatment is used consistently and appropriately.[2]

Potential benefits of TNF-blockers

The efficacy of the three anti-TNF therapies currently approved for treatment of moderate to severe psoriasis, adalimumab, etanercept, and infliximab, is well documented.[5-7] TNF blockade is generally well-tolerated and offers the potential of long-term, clinically significant improvement for patients whose disease does not respond to standard pharmacological and phototherapies. A growing body of data supports cost-effectiveness and long-term safety of the anti-TNF agents.[8,9]

Clinical Pearls

- Many psoriasis patients are not satisfied with the psoriasis control they can achieve with conventional therapies.
- Therapies that target the tumour necrosis factor (TNF) component of the chronic inflammatory cascade are excellent options for psoriasis patients.
- Treatment expectations are increasingly positive since the potential for better outcomes has been demonstrated by anti-TNF agents.
- There is no single best treatment for psoriasis; medical decision-making for moderate to severe disease is complex and the patient should be actively involved in the process.
- Educating patients about their disease, therapy and its potential side effects can help optimize treatment adherence and patient safety.



Skin clearance, patient satisfaction and improved adherence

In 67 high-need psoriasis patients, introduction of biologic treatment led to a decrease in psoriasis area and severity index (PASI) from 19.0 at the start of biologic therapy to 6.4 at analysis in 66% of subjects. Patient satisfaction with biologics was high, indicated by a mean Treatment Satisfaction Questionnaire for Medication (TSQM) version II score of 77.8.[10]

Another study reported that adherence rates were similar across the biologics, and significantly higher after the introduction of a biologic than with standard treatment with other psoriasis medications (0.66 vs 0.39; p<0.001).[11]

Reduced hospitalizations and cost-effectiveness

Based on their small study (n=67), Driessen et al concluded that biologic therapies may have cost-neutral or cost-saving effects for high needs psoriasis patients who otherwise require long hospitalization periods.[10]

A longitudinal cohort study comparing pre-and post-introduction of biologic therapy reached similar conclusions. Bhosle et al noted that compared with conventional treatment, biologics were associated with a significantly lower number of hospitalizations (p<0.001). Despite higher costs associated with prescriptions for biologics, total health care costs did not differ significantly in the post-biologics period.[11]

Effectiveness in challenging psoriatic conditions

Because of the risk of social isolation and other profound quality of life issues for patients with facial or genital psoriasis, systemic or biologic therapies should be considered if topical treatments fail.

When systemic agents are used for controlling refractory plaque psoriasis elsewhere on the body, they may have added benefits in improving scalp and nail psoriasis. The latter may be associated with significant pain, disability, and adverse psychosocial effects; conventional treatment of nails is lengthy, frequently ineffective, sometimes painful and hence, poorly adhered to. A small but growing body of evidence on the biologics suggests that patients on these therapies for skin involvement may also achieve nail benefits. Infliximab achieved complete clearance in over half of all patients with moderate to severe nail involvement in one large trial.[6,12]

Preparing your patients[20]

Pre-treatment screening

- tuberculosis (latent or active)
- hepatitis B and C
- (endemic) opportunistic infections where appropriate
- baseline (and annual) skin examinations

Patients should know about potential risks of:

- allergic reactions, acute and delayed
- infections (viral, fungal, bacterial)
- liver disease
- heart problems
- lymphoma, or other cancers
- nervous system effects
- autoimmunity
- psoriasis—worsening or changing symptoms
- vaccinations with 'live' vaccines

Rare adverse effects

Serious infections

Concerns about the effects of immunosuppression with biologics must be kept in perspective. Other than acitretin (an oral retinoid), all systemic treatments including the biologics are immunosuppressive and are contraindicated in patients with cancer or infections.[13]

What patients want to know

- Onset of action: Improvement is seen by four weeks and reductions in severity by 12 weeks.[13]
- Response rates: Up to 80% of patients may achieve a 75% reduction in their PASI (referred to as a PASI 75).[13]
- Quality of life: Quality of life is generally improved in the presence of biologic therapy for psoriasis.[14] In the EXPRESS trial, 47% of the patients in the infliximab group in achieved a Dermatology Life Quality Index (DLQI) of 0 at week 10 (placebo 1.3%), demonstrating that these patients were no longer affected by psoriasis in their daily life.[15]
- Maintenance of remission: The EXPRESS study of long-term infliximab maintenance therapy for moderate to severe psoriasis demonstrated a correlation between the absence of skin symptoms and maximum improvement in HRQL.[6,15]
- Safety in pregnancy: There has been some recent controversy about the safety of TNF-blockers during pregnancy[16] in the wake of a somewhat alarmist review of FDA adverse effect data. Evidence suggests that immunoglobulin G generated in response to anti-TNF agents such as certolizumab and infliximab is maternal in nature[17,18] and that anti-TNF agents do not cross the placenta before the 3rd trimester of pregnancy (26 weeks).[19]

Potential contributors to TNF-inhibitor related cutaneous infections[20]

- higher dose ranges
- concomitant immunosuppressive therapy
- comorbidities (including poorly controlled diabetes)

Nonmelanoma skin cancers (NMSCs) are increased in trials with TNF inhibitors, with an incidence of 0.3–1.4% (pooled data from FDA labels, a review, and a prospective study through 2005).[20]

Auto-immune adverse effects (eg, lupus erythematosus) secondary to TNF blockade are rare, affecting approximately 1% of patients; of those, 80% were being treated for rheumatoid arthritis.[20]

Comorbidities affect patient risks[21,22]

As a complex inflammatory disease, psoriasis is immunologically similar to (often comorbid) disorders such as cardiovascular (CV) disease and inflammatory arthritis **(Table 1)**.

Table 1

Relative CV risks in psoriasis versus the general population

Obesity	1.3–1.8 (depending on psoriasis severity)
Hypertension	1.2
Dyslipidemia	1.3
Diabetes	1.9 (for severe psoriasis)

Lifestyle modifications should be recommended to alleviate the potentially aggravating impact of systemic (especially conventional) treatments for psoriasis. Patients with psoriasis should be regularly counselled regarding lifestyle modification and interventions to reduce the impact of associated comorbidities and exposures known to increase malignancy including smoking, obesity and diet. A diet with a low glycemic index and low fat intake along with moderation of alcohol consumption can reduce the risk of medically significant liver-associated comorbidities.[14]

Considering concomitant medication use

Patient management can be complicated by the fact that certain psoriasis treatments may have side effects that mimic symptoms of cardiovascular conditions or exacerbate existing comorbidities **(Table 2)**. Conversely, certain drugs used to treat psoriasis comorbidities may exacerbate a patient's psoriasis. It is usually difficult to establish a firm causal link between a drug treatment and a psoriatic flare.[2]

Psoriasis patients who have been previously treated with cyclosporine and/or have received extensive UV phototherapy, particularly psoralen with ultraviolet light A (PUVA), could be at an increased risk of developing skin malignancies with anti-TNF therapy.[23,24]

Table 2

Antipsoriatic agents that may exacerbate common comorbidities[2]

Medication	Adverse reaction
Acitretin	Hypertriglyceridemia
Cyclosporine	Hypertension Hyperlipidemia
Methotrexate	Liver toxicity, fibrosis, and cirrhosis, especially in patients with comorbid diabetes or obesity

Psoriasis treatment with a side order of CV benefits?

The anti-inflammatory effects of biologic treatments may benefit patients who have risks or comorbidities that limit long term use of conventional therapies. This is particularly relevant in the presence of cardiovascular risk factors.

Studies in psoriasis and rheumatoid arthritis suggest that methotrexate (with or without folic acid)[25] or biologics may decrease CV events. A small study reported that anti-TNF therapy improved aortic stiffness in patients (n=50) with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. These findings support the idea that anti-inflammatory treatment has a favourable effect on cardiovascular risk in patients with inflammatory arthropathies.[26,27] More research is needed.

Conclusion

TNF-blockers are proving to be a valuable addition to our standard therapies for achieving and maintaining disease control in patients with moderate to severe psoriasis. Biologic therapies appear to work in these patients irrespective of their response to standard therapies. It is important to review both benefits and risks of anti-TNF agents with our patients. As we accumulate more information about the efficacy and safety of TNF blockade in the treatment of psoriasis, it is becoming increasingly evident that the risks are minimal compared to the benefits anti-TNF therapy provides to patients.

In brief: Cutaneous Vasculitis

Vasculitis is an inflammatory process directed primarily at vessels which results in the destruction of the vessel walls leading to hemorrhage, ischemia, and/or infarction.

Cutaneous vasculitis manifested as urticaria, purpura, hemorrhagic vesicles, ulcers, nodules, livedo, infarcts, or digital gangrene, is a frequent and often significant component of many systemic vasculitic syndromes.[28]

Potential mechanisms of vascular damage include:[29]

- immune complexes
- antineutrophil cytoplasmic antibodies (ANCA) (humoral)
- T-lymphocyte responses and granuloma formation (cell mediated)

Classification of cutaneous vasculitis

Vasculitis may occur as a primary phenomenon (eg, idiopathic cutaneous leukocytoclastic angiitis) or as a secondary disorder (eg, connective tissue disease). Initial classification is based on the size of the predominant vessel affected (large, medium, small), and extent of skin and subcutaneous involvement. Finally, classification should incorporate pathophysiologic markers such as direct immunofluorescence (DIF) and ANCA.[28]

Biopsy (Bx) will reveal dermal small-vessel inflammation, often with leukocytoclasis. Deeper biopsy specimens – extending to the subcutaneous tissue and taken from the most tender, reddish, or purpuric skin lesions – may show coexistence of pandermal, small-vessel vasculitis and subcutaneous medium vessel vasculitis.[28]

The diagnostic yield of a skin biopsy (Bx) is greatly influenced by the depth of the Bx. In general, a punch or incisional biopsy extending into the subcutis is the preferred means for sampling a vasculitic lesion in order to sample vessels of all sizes.

As shown in **figure 1**, Henoch-Schönlein purpura (HSP) and cutaneous leukocytoclastic angiitis (CLA) generally affect the superficial vessels of the skin whereas polyarteritis nodosa (PAN), nodular vasculitis (Nod Vas), and giant cell arteritis (GCA) affect deep muscular vessels found at the dermal-subcutis interface and within the subcutis. Most other forms of vasculitis such as cryoglobulinemic vasculitis (CV), connective tissue disease (CTD) vasculitis, and ANCA-positive vasculitis can affect both small and muscular vessels (although not necessarily in the same biopsy).[28]

Differentiation of vasculitis types[31]

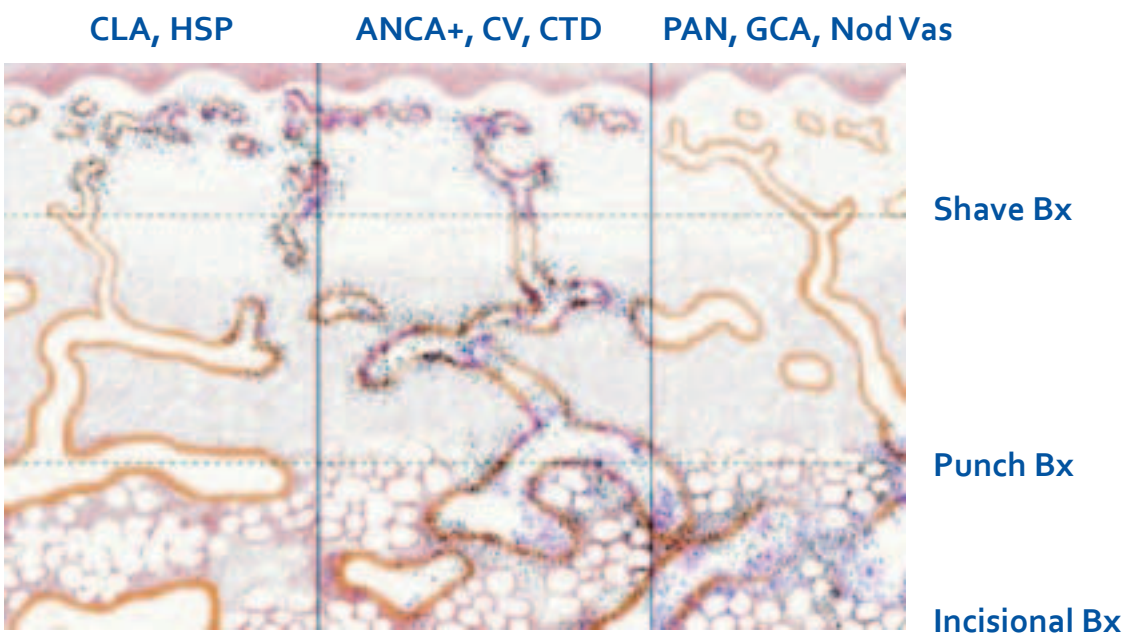
Measurement of serum antineutrophil cytoplasmic antibodies (ANCA) levels detects:

- myeloperoxidase-ANCA +:⟶ Churg-Strauss syndrome or microscopic polyangiitis
- proteinase 3-ANCA +: ⟶ Wegener's granulomatosis
- cryoglobulin +:⟶ cryoglobulinemic vasculitis

Direct immunofluorescence (DIF) of skin biopsy specimen detects:

- immunoglobulin A deposition ⟶ Henoch-Schönlein purpura

Figure 1[30]



- presence of anti-phosphatidylserine-prothrombin complex antibodies and/or lupus anticoagulant and leukocytoclastic vasculitis in the upper to middle dermis → cutaneous leukocytoclastic angiitis
- presence of necrotizing vasculitis in the lower dermis and/or associated with subcutaneous fat → cutaneous polyarteritis nodosa

Treatment of cutaneous vasculitis[28,29]

- Treatment depends on the etiology and extent and severity of disease. Cutaneous vasculitis often represents a self-limited, single-episode phenomenon which responds to general treatment measures such as leg elevation, warming, avoidance of standing, cold temperatures and tight fitting clothing, and therapy with antihistamines, aspirin, or nonsteroidal anti-inflammatory drugs.
- More extensive therapy such as low-dose prednisone (monotherapy not recommended) plus other immunosuppressive and cytotoxic drugs such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, or mycophenolate mofetil is indicated for symptomatic, recurrent, extensive, and persistent skin disease or coexistence of systemic disease.
- Biologics including tumor necrosis factor (TNF)-alpha inhibitor infliximab and the anti-B-cell antibody rituximab appear to be beneficial in Wegener's granulomatosis, Behçet's disease, cryoglobulinemic vasculitis, and ANCA-associated vasculitis. In severe ANCA-associated vasculitis, rituximab has been shown to be non-inferior to daily cyclophosphamide for induction of remission and may be superior in relapsing disease.[32,33]

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