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Combination Therapy of Biologics with Traditional Agents in Psoriasis

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ABSTRACT

Although biologics are very efficacious as monotherapy in patients with psoriasis, combination treatment with traditional systemic and topical therapies may increase the speed of onset and enhance efficacy without significant additional toxicity. In contrast, in psoriatic arthritis, the addition of methotrexate to anti-tumour necrosis factor-alpha therapy does not enhance efficacy in either the skin or joints.

Key words: acitretin, adalimumab, alefacept, biologics, calcipotriol, combination therapy, cyclosporine, etanercept, infliximab, methotrexate, phototherapy, psoriasis

Introduction

Psoriasis is a chronic inflammatory disorder that is associated with a number of comorbidities including arthritis, cardiovascular risk factors, and inflammatory bowel disease.[1] Patients with moderate to severe disease usually require phototherapy, traditional systemic medications (e.g. methotrexate, acitretin, and cyclosporine), or biologic agents (e.g., adalimumab, alefacept, etanercept, infliximab, and ustekinumab) for adequate control.[2] Alefacept binds to CD2 on CD45RO+ effector T lymphocytes, inhibiting their activation and inducing apoptosis of these T cells, while adalimumab, etanercept, and infliximab inhibit tumour necrosis alpha, a cytokine that is elevated in patients with psoriasis, and ustekinumab inhibits interleukins 12 and 23, which are also elevated in psoriasis.[3] Although biologics are generally used as monotherapy, in Europe the concurrent use of traditional systemic agents can be found in up to 30% of cases.[4] Addition of a biologic to traditional systemic therapy can enhance efficacy, or permit discontinuation or dose reduction of the traditional systemic agent without compromising disease control. On the other hand, addition of a systemic agent, phototherapy, or topical therapy to a biologic can enhance efficacy, including speed of onset, degree of clearing, and in some cases duration of remission or improve safety. Since acitretin can suppress the development of skin cancers, such as squamous cell carcinoma in high risk patients,[5] addition to at-risk individuals receiving biologic treatment might enhance safety.

In rheumatoid arthritis (RA) and psoriatic arthritis patients, methotrexate is routinely used with tumour necrosis factor-alpha (TNF-alpha) inhibitors without additional toxicity.[6,7] In contrast to the psoriasis and RA investigations, studies in patients with psoriatic arthritis have shown that concurrent methotrexate and anti-TNF agents (adalimumab,[8] etanercept,[9] infliximab[10]) does not enhance efficacy in either the skin or joints. Some efficacy and safety data in psoriasis are available for combination therapy with adalimumab, alefacept, etanercept, and infliximab, but not for ustekinumab.

Combination Therapy with Adalimumab (Humira®)

Calcipotriol + Betamethasone Dipropionate

Adalimumab used in combination with calcipotriol + betamethasone dipropionate (Dovobet®) showed a more rapid and higher PASI 75 response at week 4 (40.7% vs. 32.4%, p=0.021) compared with adalimumab monotherapy.[11] However, at week 16, there was no significant difference in PASI 75 response (64.8% with combination therapy vs. 70.9% with adalimumab monotherapy, p=0.086).

Methotrexate

Adalimumab in combination with methotrexate results in down regulation of more inflammatory markers in psoriatic plaques than monotherapy with either agent.[12] In the ADEPT psoriatic arthritis trial, at week 48, PASI 50, 75, 90, and 100 response rates were greater in the with-methotrexate subgroups (n=29)

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compared to the adalimumab without methotrexate subgroup (n=40), but only the PASI 50 results were statistically significant (PASI 50 in 83% vs. 55 %, p<0.05).[13]

Combination Therapy with Alefacept (Amevive®)

Alefacept has Health Canada approval for use in combination with mid- to high-potency topical agents, ultraviolet B (UVB) phototherapy, methotrexate, cyclosporine, and systemic retinoids.[14] The Canadian AWARE study showed that alefacept allowed for a reduction in dosage or discontinuation of concomitant systemic agents or phototherapy.[15]

In an open-label study of 1-3 courses of alefacept (n=449), combination therapy with topical agents occurred in approximately one-third and combination treatment with phototherapy or traditional systemic agents was also used in approximately one-third of patients [UVB (n=24), methotrexate (n=63), cyclosporine (n=42), systemic retinoids (n=23), and prednisone (n=7)].[16] When alefacept was added to existing treatment regimens, ≥30% achieved a response of mild or better. Concurrent therapy with methotrexate or cyclosporine resulted in lower response rates than with other agents. A physician global improvement (PGA) of at least two categories was achieved by 20-21% on methotrexate, 31-43% on cyclosporine, 50-64% on systemic retinoids, 43-62% on mid- to high-potency topical agents, and 55-77% on UVB. There was no increased risk of infection or malignancy when alefacept was used in combination with methotrexate or cyclosporine. The lower response rates with methotrexate combination therapy may be secondary to the study requirement for discontinuation of methotrexate within 4 weeks of initiation of alefacept and the fact that many patients experienced flares as soon as it was discontinued. Cyclosporine was also initially suspended within the first 4 weeks of alefacept therapy; however, due to flares, the protocol was amended so that cyclosporine could be discontinued within 6 weeks after the 12-week alefacept dosing period. Other therapies could be continued throughout the treatment courses.

UVB Phototherapy

In an open label study of 60 patients, greater efficacy and a more rapid onset of action were noted with a combination of alefacept and narrowband (nb) or broadband (bb) UVB compared with alefacept monotherapy.[17] Four weeks after treatment was started, PASI 50 was achieved at the US site in 0% on monotherapy vs. 22% on bb UVB + alefacept, and at the French site 44% on monotherapy vs. 82-90% on nb UVB + alefacept. Similarly in a half-side comparison alefacept/nb UVB study (n=14), the side treated with nb UVB had accelerated and improved clearance.[18]

Acitretin

A case series of two patients who had previously been unresponsive to ultraviolet phototherapy, methotrexate, and acitretin showed that combination therapy of alefacept with low dose (10 mg, 25 mg) acitretin shortened the onset of improvement to 4-5 weeks (compared with the usual 8 weeks) and improved inverse and palmoplantar psoriasis.[19] In one patient with a history of squamous cell carcinoma (SCC) who developed three SCCs every 2 weeks while on etanercept monotherapy, after acitretin 25 mg every other day was added only actinic keratoses developed during the 18 month follow-up.[20]

Combination Therapy with Etanercept (Enbrel®)

Calcipotriol

The addition of calcipotriol cream twice daily for 4 weeks, then once daily for 8 weeks, in patients with psoriasis and psoriatic arthritis who had not achieved PASI 50 at week 12 (n=45 patients) with etanercept 50 mg twice weekly, allowed 31.1% (14 patients) to become PASI 75 responders and 51.1% (23 patients) to become PASI 50 responders at week 24 despite a dose reduction in etanercept to 25 mg twice weekly at week 12.[21]

Phototherapy

Narrowband UVB enhances efficacy irrespective of whether it is used from the start (12 week PASI 75 in 90% vs. 40% on etanercept 25 mg twice weekly monotherapy)[22] or added after 6 weeks to patients who had not attained PASI 75 response with etanercept 50 mg twice weekly (after 6 weeks of combination therapy: mean PASI=1.6 vs. 4.7 for non-UVB treated body half, p=0.0192).

Methotrexate

In the EASE trial, the odds ratio of a 'clear'/'almost clear' PGA was 2.246 (95% confidence interval (CI) 1.25, 4.0; p=0.0069) for concomitant methotrexate/etanercept when compared with etanercept monotherapy.[23] In this study, 30% of patients could reduce their weekly dose of methotrexate and 16% could stop it altogether. In the EDUCATE study, 29% could discontinue methotrexate and 7% could lower their dose.[24] In cases of inadequate response to methotrexate, in one study continuation of the methotrexate when etanercept was initiated resulted in greater efficacy with a similar safety profile than when the methotrexate was tapered and discontinued during the first 4 weeks (PGA 'clear' or 'almost clear' at 24 weeks in 66.7% vs. 37.0% respectively, p=0.025).[25]

Acitretin

A small study (n=60) showed that etanercept 25 mg twice weekly and etanercept 25 mg once weekly + acitretin 0.4 mg/kg/day had similar efficacy at week 24 (PASI 75: 45% and 44% respectively; mean BSA reduction: 80% and 78.2% respectively), suggesting that concomitant use of acitretin can lower the required dose of etanercept.[26]

Cyclosporine

Small case series suggest that etanercept can maintain control when cyclosporine discontinuation is needed.[23,27] In a small psoriatic arthritis study, addition of cyclosporine 3.0 mg/kg/day to 11 patients whose arthritis was in remission, but who had an insufficient skin response, resulted in 9/11 achieving PASI 75 at week 24.[28]

Combination with Infliximab (Remicade®)

Warren et al. used methotrexate in one patient and cyclosporine in two patients at transition to infliximab therapy in order to prevent a flare.[29] Dalaker and Bonesrønning treated 17 patients with infliximab 3 mg/kg + methotrexate 7.5-15 mg/wk, one with infliximab 5 mg/kg + methotrexate, and five patients with infliximab 5 mg/kg + azathioprine 50 mg/day.[30] At week 14, 69.6% achieved PASI 75 and 39.1% PASI 90. Two patients on methotrexate + infliximab stopped treatment because of loss of response, one after 14 months and one after 3 years.

Methotrexate

The National Institute for Health and Clinical Excellence (NICE) guidelines recommend concurrent use of methotrexate with infliximab to enhance efficacy, reduce the development of antibodies to infliximab, and in cases where it is need, to associated arthritis.[31] Co-administration of methotrexate with infliximab may result in higher infliximab serum levels.[31]

Conclusions

Combination therapy of biologics with topicals, phototherapy, and/or traditional systemics is commonplace and may enhance efficacy including speed of onset and maintenance of response. Moreover, biologics can permit discontinuation or dose reduction of traditional systemic agents. Conversely, traditional systemic agents may permit lowering of the biologic dose. Rather than changing biologic agents, combination therapy should be considered in circumstances of inadequate efficacy or relapses/flares with monotherapy.

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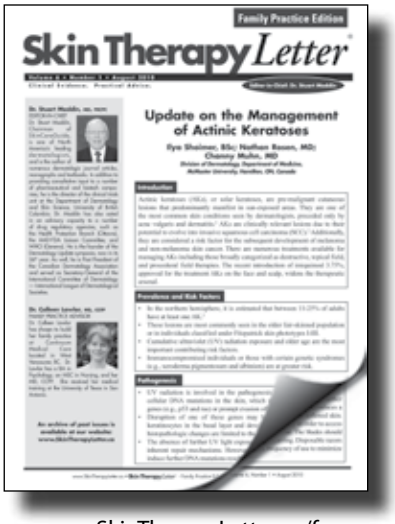

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Bedbugs: An Update on Recognition and Management

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ABSTRACT

The common bedbug (Cimex lectularius) *is increasingly prevalent and a source of concern and questions for patients. In addition to a range of cutaneous presentations and potential for serious sequelae, bedbug bites cause significant psychological distress and create an economic burden associated with infestation control. Recognition of characteristic entomology, clinical presentation, diagnostic features and differential diagnosis can support expedient identification of patients exposed to infestations and support their appropriate management.*

Key words: bedbugs, *Cimex lectularius*, infestation, pest control

Introduction

The common bedbug, *Cimex lectularius* (*C. lectularius*), is a hematophagus arthropod. A pest to mankind for centuries, bedbug populations in industrial nations declined steadily with the advent of novel pesticides, improved sanitation practices, and economic conditions.[1] In contrast, infestations in developing countries have persisted.[2] However, pest control companies in Canada and the United States are reporting overwhelming increases in the number of new bedbug encounters compared with 10 years ago.[3] This recent bedbug resurgence has been attributed to evolving pesticide resistance coupled with increased rates of international trade and travel, as travellers can bring the insects home in their clothing and luggage.[4,5] Bedbugs have since established more widespread infestation of environments serving transient populations such as hotels, dormitories, hospitals, cruise ships, and homeless shelters.[6-9] In addition to this increased prevalence, bedbugs are also widely discussed in popular media and may be presented as a concern by patients.[10] Awareness of the entomology, diagnosis, and management of bedbugs can assist physicians in detecting affected individuals and providing concerned patients with education on this topic.

Epidemiology

Bedbugs can be introduced to an environment from either local or distant sites. Local transmission occurs by "active dispersal" as the insects walk short distances to find a source for feeding. This is the predominant means of infestation in multi-unit dwellings as the bedbugs travel through ductwork, crevices in drywall, or electrical outlets. Infestation from distant sites occurs via "passive dispersal" when bedbugs travel on clothing, luggage, or shipped furniture.[11] As such, poorly maintained living conditions, overcrowding and transitory populations can confer increased risk of bedbugs.[12] Local public health departments often have limited resources to combat this problem, and municipal regulatory bodies struggle to assign responsibility of high eradication costs to landlords or transient tenant populations. [13]

Entomology

Bedbugs are broad, oval-shaped, flat, wingless insects.[14] Adults are red-brown in color and typically measure 4-7 mm; they are often likened to apple seeds in their appearance.[11] Patients may describe a distinctive, characteristic 'sweet' odor associated with the insects. While they may be difficult to detect early in the course of infestation, the bedbug life cycle can result in an exponential increase in numbers during the first month. The typical lifespan in temperate climates averages from 6 to 24 months, and an adult female could lay 200-500 eggs during this time.[15] Nymphs hatch after 4 to 10 days and are pale and translucent. To reach full maturity they must molt four times, which can only occur with a blood meal. If a host is available they will feed every 3 to 7 days.[15] However, adding to their resilience, bedbugs can survive 12 months without feeding, and even more than 2 years in cooler environments.[11]

Hosts are typically bitten at night on exposed skin and an insect will feed for 10 to 20 minutes until completely engorged.[15] The proboscis, an elongated feeding organ, is composed of two tubules. The first tubule secretes several substances, including an anesthetizing compound (producing a painless bite that may be undetectable for hours), proteolytic enzymes, anticoagulants (such as factor-X inhibitor), and vasodilatory substances (such as nitric oxide).[16] This collection of substances can contribute to the subsequent local hypersensitivity reactions.[11] The second tubule simultaneously extracts the blood meal.

Bedbugs do not stay on the body of the host after feeding. Unable to fly or jump, they have six legs with which they are able to travel into crevices and evade detection at ambient temperatures.[17] While they are most active in temperate environments, bedbugs exhibit incredible tolerance for temperature extremes and have been demonstrated to require 1 hour of exposure to temperatures lower than -16°C or greater than 48°C in order to be killed.[18,19]

Psychological Consequences

The social and psychological impact of bedbugs can be devastating for affected individuals. Infestation can be stigmatizing due to the misconception that bedbugs are related to poor housekeeping or inadequate hygiene. In reality, bedbugs are attracted to carbon dioxide and body heat and they are nourished by blood, not excrement or waste.[6] Minimizing clutter can thus reduce hiding places where insects may remain undetected, but patients can be reassured that they are not to blame. In addition to the stresses of identifying and controlling bedbugs in the home or workplace, some patients suffer anxiety due to fears of re-infestation even after the insects have been eliminated.[20] Extreme cases can result in delusions of parasitosis and in these situations a referral to psychiatry can be helpful.[21]

Cutaneous Manifestation

The bites of bedbugs can closely resemble those of other arthropods; however, they tend to be clustered on skin that is freely exposed when sleeping, such as the face and distal extremities. Bites may follow a linear path, or characteristically, appear in a group of three to five (colloquially known as 'breakfast, lunch, and supper').[22,23] In non-sensitized individuals, pruritic, erythematous macules may be the only cutaneous evidence of bedbug bites.[24] Bite sites typically appear as pruritic papules and wheals, which form in response to components of the saliva injected by the bedbug. The lesions often have a hemorrhagic punctum in the centre. Exaggerated local reactions, such as wheals, vesicles and bullae, may occur in patients whom have previously been bitten or have been sensitized to other insects.[25-27] Papular eruptions that mimic urticaria have been associated with IgG antibodies to *C. lectularius* proteins.[28,29] However, compared with other causes, urticaria from bedbugs has been found to last longer and blanches less easily.[29] In contrast, it is IgE that mediates the occasionally-manifested bullous allergic hypersensitivity.[22] Although rare, cases of asthma exacerbations, type I hypersensitivity allergic cutaneous reactions, and severe anemia secondary to bedbug bites have been reported.[25,30]

Diagnostic Considerations

Differential Diagnosis

Insect bite reactions are often non-specific and, as such, are susceptible to misdiagnosis. In the absence of typical presentation or evidence of infestation, bedbug bites can be challenging to differentiate from those of other arthropods. Further, in addition to the common bedbug *C. lectularius*, the tropical bedbug *Cimex hemipterus* and bat bug *Cimex pipistrelli* cause similar clinical symptoms.[31] Bites from bedbugs have been incorrectly diagnosed and documented as:[4]

- Mosquito bites
- Spider bites
- Scabies
- Drug eruption
- Food allergy
- Staphylococcus infection
- Varicella

Unfortunately, misdiagnosis can result in inappropriate or unnecessary therapeutic and investigative interventions. While bedbugs characteristically affect skin that is exposed during the night, the furrows of scabies are more often found in covered areas, such as the periumbilical region, scrotum, and axillae.[14] There is a broad differential in which histology may distinguish other conditions that produce similar-appearing skin lesions, including dermatitis herpetiformis, transient acantholytic dermatosis, urticarial dermatoses, or prodromal bullous pemphigoid.[14,32]

Histology

In the event of biopsy, bedbug reactions are similar histologically to other arthropod bite reactions. Tissue demonstrates dense eosinophil-predominant perivascular infiltrate of both superficial and deep dermis with minimal spongiosis. Subepidermal vesiculation and edema of the papillary dermis may also be seen.[14,29,32]

Disease Transmission

In addition to cutaneous and possible allergic reactions to bedbugs, the risk of disease transmission via bites has also been raised as a concern.[33] There is both historical and experimental laboratory data supporting the Hepatitis B virus as a candidate for bedbug transmission.[34] Further, a recent case report details the isolation of both vancomycin-resistant *Enterococcus faecium* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) bacterial colonies from bedbugs.[35] However, although the question of the hematogphagus bedbug vectorial capacity is compatible with logic and these parasitic insects have been found to carry >40 different microorganisms, they have not been identified as transmitting human disease.[11,26]

Management

Uncomplicated bedbug bites usually resolve within 1-2 weeks and are self-limited. Although the evidence base is weak, management is otherwise symptomatic. Topical or oral antipruritic agents combined with an intermediate corticosteroid can bring some relief. For some patients, having prescription topicals compounded with menthol and camphor can be soothing. Superinfection can occur, especially in cases with significant excoriation, and can be treated with topical or oral antibiotics.[16]

Systemic reactions to bedbug bites are treated with intramuscular epinephrine, antihistamines, and oral corticosteroids, as in insect-induced anaphylaxis.[16]

In tandem with the control of symptoms, eliminating the infestation must be aggressively pursued to prevent further bites. Goddard et al. (2009) have outlined several steps that are useful in successful eradication of bedbugs:[16]

1. Proper identification of the bedbugs species
2. Education of the patient, other dwelling occupants, and landlord, as applicable
3. Thorough inspection of both infested and other nearby areas
4. Implementation of pesticide and non-chemical control measures
5. Follow-up to ensure control of the infestation

Conclusion

Bedbug infestation is increasingly prevalent and generates much anxiety in patients, which is fuelled by media coverage of this issue. As such, bedbug bites are a prudent component of a differential diagnoses if arthropod bites are suspected or history

is suspicious for infestation. Confirmation of infestation may be necessary to establish the diagnosis in light of the often equivocal constellation of clinical symptoms. In addition to the cutaneous discomfort of bites and potentially serious sequelae, such as anaphylaxis, bedbug bites can cause significant psychological distress. Controlling symptoms through corticosteroids and anti-pruritics is helpful for patient comfort. However, ultimately, eradication of the offending insect and the prevention of further bites is the goal of therapy for these patients.

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Update on Drugs

Name/Company	Approval Dates/Comments
Peginterferon alfa-2b *Sylatron*™ Merck & Co Inc. Schering Corporation	The US FDA approved peginterferon alfa-2b in March 2011 to treat node-positive melanoma after surgical resection. Therapy is administered subcutaneously (may be self-injected) and is indicated as an adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection. The recommended dosing is 6 mcg/kg/week subcutaneously for 8 doses, followed by 3 mcg/kg/week subcutaneously for up to 5 years. A clinical investigation showed that patients who received the drug delayed cancer recurrence by approximately 9 additional months. One-third of peginterferon alfa-2b-treated patients ceased therapy due to adverse effects.
Imiquimod 3.75% cream *Zyclara*® Graceway Pharmaceuticals	The US FDA approved this immune response modifier in March 2011 for the topical treatment of external genital warts and perianal warts in patients ≥12 years of age. Under clinical investigation, Zyclara® showed that the once-daily treatment regimen for up to 8 weeks was safe and provided sustained efficacy. Only 15% of imiquimod-treated patients with complete clearance experienced recurrence 12 weeks after therapy.
Adapalene 0.1% + benzoyl peroxide 2.5% gel *Tactuo*™ Galderma Canada Inc.	Health Protection Branch (HPB) of Health Canada approved a novel once-daily retinoid + benzoyl peroxide combination gel in March 2011 for the treatment of mild to moderate acne vulgaris in patients ≥12 years of age. The product is marketed in the US under the trade name of Epiduo®, which was FDA approved in December 2008.
Collagenase clostridium histolyticum *Xiapex*® Pfizer Inc. BioSpecifics Technologies	The European Medicines Agency (EMA) approved this novel, first-in-class biologic in March 2011 for the treatment of Dupuytren's contracture in adults with a palpable cord. The injected enzymes dissolve and weaken the contracted collagen cord. It is the only nonsurgical option for Dupuytren's disease.

Generic Drug Update	
Minoxidil 5% foam Perrigo Company	The US FDA approved a generic version of OTC minoxidil foam in May 2011 for hair regrowth (innovator brand Men's Rogaine® Foam, McNeil-PPC, Inc.).
Imiquimod 5% cream Taro Pharmaceutical Industries Ltd.	The US FDA approved a generic version of imiquimod 5% cream in April 2011 for the topical treatment of actinic keratoses on the face or scalp, superficial basal cell carcinoma, and external genital and perianal warts in patients ≥12 years of age (innovator brand Aldara® 5% cream, Graceway Pharmaceuticals).
Famciclovir tablets Mylan Pharmacetuicals, Inc.	A generic formulation of famciclovir (innovator brand Famvir®, Novartis Pharmaceuticals) was launched in April 2011 for the treatment of herpes zoster (shingles).
Valacyclovir hydrochloride tablets Actavis Group	The US FDA has granted approval to Actavis Group in March 2011 to market its generic version of GlaxoSmithKline's antiviral product valacyclovir hydrochloride (Valtrex®) tablets for the treatment of herpes zoster and genital herpes.