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Review

Systemic therapies in vitiligo: a review

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Introduction

Vitiligo is characterized by the loss of epidermal melanocytes. First, melanocytes are damaged, possibly by oxidative stress. This triggers the autoimmune pathway, resulting in melanocyte destruction, leaving the follicular and cutaneous melanocyte reservoir unable to keep pace.¹

Prompt and aggressive treatment of vitiligo is important, as it can affect the quality of life, and early treatment may prevent progression.² Many patients with active disease and extensive body surface area (BSA) involvement may benefit from systemic therapy. Interest in this area has grown as clinicians search for novel therapies to improve patient outcomes. Here, we review systemic therapies in vitiligo including immunosuppressants and other more novel agents, including antibiotics, antioxidants, and hormone analogues. There are some limitations in comparing studies since outcome measures were not standardized.

Abstract

Vitiligo is characterized by the development of depigmented macules and patches. Autoimmunity has been established as a factor in disease pathogenesis, leading to utilization of immunosuppressive agents. Topical immunosuppressants are commonly used; however, this treatment modality is often cumbersome and inefficient, as many patients have active disease with extensive body surface area involvement. Prompt and aggressive treatment of vitiligo is important, as this may prevent progression and improve quality of life. To meet these challenges and improve patient outcomes, interest in systemic therapies has grown. Currently, oral therapies are rarely prescribed, likely due to concerns with systemic side effects and unclear efficacy. This article provides a brief overview on the use of systemic agents in treating vitiligo in order to provide additional therapeutic options to clinicians.

Immunosuppressants**Oral corticosteroids***Mechanism of action*

Systemic corticosteroids, used for decades in vitiligo, are a first-line option for rapidly progressing disease.³

Corticosteroids bind cytoplasmic receptors, which regulate gene transcription of the inflammatory pathway⁴ causing the production of anti-inflammatory proteins, leading to the inhibition of autoantibody formation and cytotoxic T-cell apoptosis. Patients with vitiligo have decreased serum melanocyte autoantibodies and antibody titers to melanocyte surface antigens after treatment with corticosteroids (Fig. 1a).⁵

Application

Pasricha and Khaitan used oral mini pulse (OMP) therapy in patients with extensive or rapidly spreading vitiligo to minimize

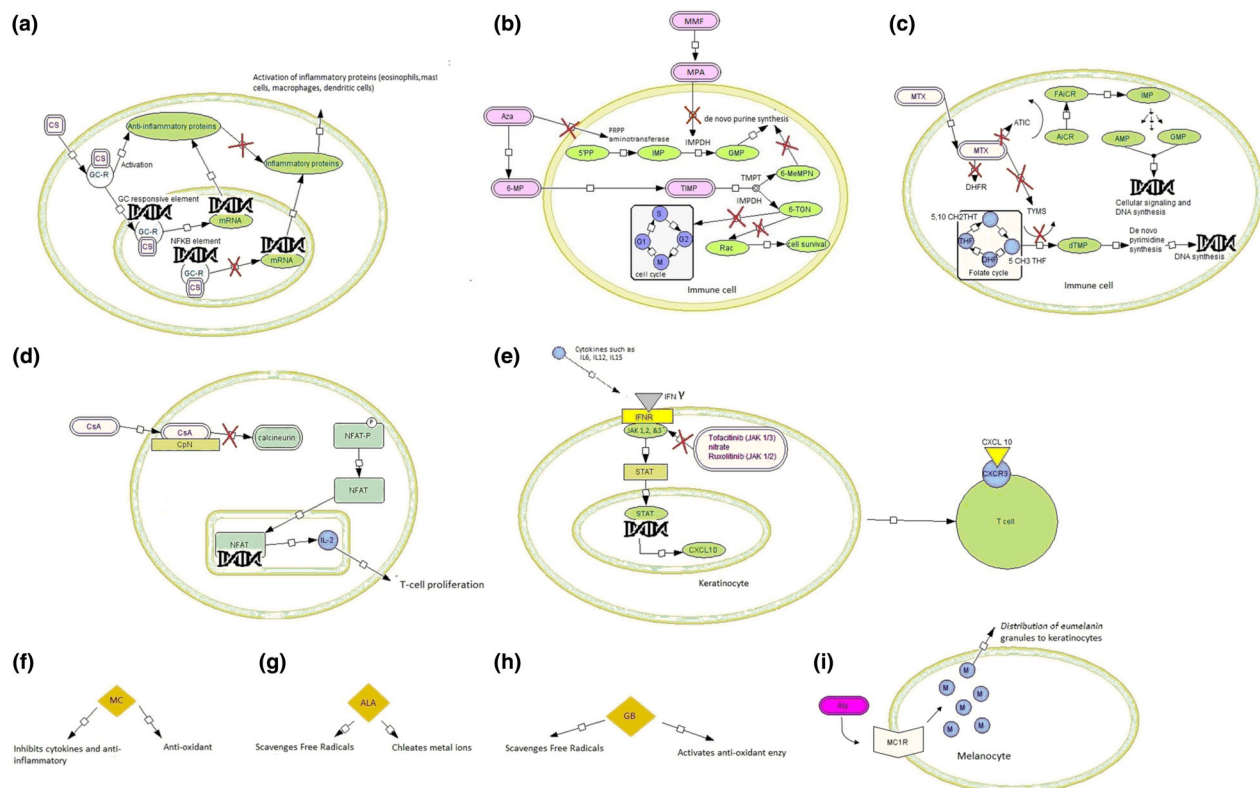


Figure 1 Intracellular pathways of systemic therapies in vitiligo: (a) corticosteroids, (b) azathioprine and mycophenolate mofetil, (c) methotrexate, (d) cyclosporine A, (e) ruxolitinib and tofacitinib nitrate, (f) minocycline, (g) alpha-lipoic acid, (h) ginkgo biloba, and (i) afamelanotide. Abbreviations: 5'PP, 5-phosphoribosyl - α -pyrophosphate; 6-MeMPN, 6-methyl mercaptopurine nucleotides; 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine nucleotides; Afa, afamelanotide; AiCR, 5-aminoimidazole-4-carboxamide ribonucleotide; ALA, alpha-lipoic acid; AMP, adenosine monophosphate; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase; Aza, azathioprine; CpN, cyclophilin; CS, corticosteroids; Csa, cyclosporine A; DHF, dihydrofolate; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; FAiCR, 10-formyl 5-aminoimidazole-4-carboxamide ribonucleotide; GB, ginkgo biloba; GC-R, glucocorticoid receptor; GMP, guanosine monophosphate; GMPS, guanosine monophosphate synthetase; HGPRT, hypoxanthine phosphoribosyl transferase; IFN- α , interferon- α ; IFNR, interferon- α receptor; IL-2, interleukin-2; IMP, inosine monophosphate; IMPDH, inosine monophosphate dehydrogenase; MC, minocycline; MC1R, Melanocortin 1 receptor; MTX, methotrexate; MPA, mycophenolic acid; MMF, mycophenolate mofetil; NFAT, nuclear factor of activated T cells; THF, tetrahydrofolate; TIMP, thioinosine monophosphate; TYMS, thymidylate synthase

side effects. Five milligrams of betamethasone administered on 2 consecutive days halted disease progression within 1-3 months in 89% of the 40 patients, with some experiencing variable repigmentation. Two patients improved only after increasing the dose to 7.5 mg.⁶

In 29 patients, 25 of whom had progressive vitiligo and four had stable disease, 22 of 25 (88%) patients with active vitiligo experienced an arrest in activity after receiving 10 mg dexamethasone on 2 consecutive days, although repigmentation was minimal.⁷

When low-dose OMP therapy at 2.5 mg dexamethasone on 2 consecutive days in patients with progressive, unstable vitiligo was used, 408 of 444 (91.8%) patients achieved disease stability after a mean duration of 13.2 weeks. The remaining 36 patients (9.2%) reported a decrease in new lesions. Some repigmentation of lesions was seen in all patients after a mean of 16 ± 5.9 weeks.⁸

Kim et al. used daily low-dose oral prednisolone (0.3 mg/kg body weight) in 81 patients with active vitiligo. After 4 months, stabilization was observed in 87.7% of patients and repigmentation in 70.4%. Better repigmentation outcomes occurred in males, age 15 or younger, and disease duration under 2 years.⁹

The literature suggests that at least 3-6 months of treatment is required and can be reinitiated for relapse or combined with phototherapy.⁵ However, uniform outcome measures have not been applied.

Side effects

There are many significant side effects, especially with daily use, but these are decreased with OMP therapy.⁸ Side effects in the above studies ranged from 9% to 69% of patients, including weight gain, dysgeusia, acne, insomnia, headache, generalized weakness, agitation, menstrual disturbance, and hypertrichosis (Table 1).⁶⁻⁸

Azathioprine

Mechanism of action

Azathioprine (AZA) suppresses DNA and RNA synthesis, inhibiting B- and T-cell proliferation and function. It most potently affects lymphocytes, as they lack a salvage pathway and rely on de novo purine synthesis (Fig. 1b).¹⁰

Application

AZA was used with psoralen plus ultraviolet A (PUVA) in 60 patients randomized to receive both AZA (0.6-0.75 mg/kg) and PUVA (group 1) or PUVA alone (group 2) over a 4-month course. Group 1 achieved earlier repigmentation in a predominantly perifollicular pattern (after an average of five versus eight sessions in group 2) and a twofold greater total mean repigmentation (58.4% versus 24.8%, $P < 0.001$). Furthermore, in group 1, 30% of patients achieved 75% or greater repigmentation, compared to none in group 2. This suggests that concomitant use of AZA and PUVA leads to greater and earlier repigmentation than PUVA alone.¹¹

Patra et al. conducted a randomized comparative trial of betamethasone OMP therapy (group 1) vs. AZA (group 2) in progressive nonsegmental vitiligo. OMP halted disease progression faster than AZA, with 82.3% (19) of patients in group 1 versus 18.2% (4) in group 2 at 2 months. However, at 6 months, there was no significant difference in stabilization. Repigmentation with good color match was observed in 84.2% of patients in the OMP group versus 61.1% of patients in the AZA group.¹²

Side effects

AZA is generally well tolerated, but patients with lighter skin phototypes are at greater risk for nonmelanoma skin cancers, especially with use over 1 year (Table 1).¹³ AZA is not recommended during pregnancy (Table 2).¹⁴⁻¹⁹

Mycophenolate mofetil

Mechanism of action

Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, inhibits inosine-5'-monophosphate dehydrogenase (IMPDH), specifically the type II isoform located in lymphocytes. IMPDH is required for de novo synthesis of guanine nucleotides and, subsequently, DNA synthesis.²⁰ MMF preferentially targets B and T lymphocytes as they are dependent on de novo purine synthesis, thereby decreasing cell-mediated responses and antibody formation (Fig. 1b).^{20,21}

Application

To assess the efficacy of oral MMF as a non-steroid option in stabilizing active vitiligo, Bishnoi et al. conducted a randomized study with 50 patients with a baseline vitiligo disease activity (VIDA) score of 4.²² Group A received 2.5 mg of dexamethasone on 2 successive days of the week, and group B received

up to 2 g of MMF for 180 days with a 90-day treatment-free period. The average time to halt disease progression was 47.2 ± 2.1 days in group A and 52.5 ± 9.3 days in group B ($P = 0.21$).²² However relapse occurred earlier and was higher with MMF, but only the former was significant.²²

Side effects

Side effects include dose-dependent gastrointestinal symptoms including diarrhea, nausea, and abdominal pain, etc. Less likely are hematologic side effects including anemia, leukopenia, and thrombocytopenia (Table 1).²¹

Methotrexate

Mechanism of action

Methotrexate interferes with DNA synthesis and induces apoptosis in active CD4⁺ T cells.²³ It reduces pro-inflammatory cytokines (IL-1, IL-6, and tumor necrosis factor- α), decreases the gene expression of IL-2 and IFN- γ , and increases the gene expression of anti-inflammatory cytokines (IL-4 and IL-10).²⁴ Many of these cytokines, like IL-6 and IL-2, may be dysfunctional in vitiligo (Fig. 1c).²³

Application

Six patients with at least 6% BSA involvement took oral methotrexate (25 mg/week) for 6 months with no changes in pigmentation.²⁵ In contrast, a patient with rapidly progressing vitiligo and rheumatoid arthritis was started on oral methotrexate (7.5 mg/week). Improvement in arthritis, stability of vitiligo, and marked repigmentation were observed after 3 months of therapy.²⁶

Another study compared methotrexate with OMP corticosteroid therapy in patients with unstable vitiligo. Group 1 received methotrexate (10 mg/week), while group 2 received dexamethasone 2.5 mg on 2 consecutive days (5 mg/week). Over 24 weeks, 76% (19/25) of patients in group 1 stabilized, with 44% (11/25) achieving variable repigmentation. In group 2, 72% (18/25) of patients stabilized, with 60% (15/25) achieving variable repigmentation. The differences between the two groups were not statistically significant, demonstrating that methotrexate was not inferior and may be useful when corticosteroids are contraindicated.²³

Side effects

At dermatologic doses, side effects include increased risk of infection, gastrointestinal symptoms, elevations of liver function tests, headache, and leukopenia (Table 1).²⁷

Cyclosporine

Mechanism of action

Cyclosporine binds cyclophilin to inhibit calcineurin, which activates nuclear factor of activated T cells, a transcription factor

Table 1 Systemic therapies for vitiligo: monitoring and side effects

Generic Name (Alternative Brand Names)	Baseline Laboratory Studies and Monitoring	Ongoing Monitoring*	Comments	Representative Side effects†
Afamelanotide ⁶⁴	None	None		Erythema, mild infection, nausea, and hyperpigmentation
Alpha-lipoic acid ⁵³ Azathioprine (Imuran) ¹³	None CBC, CMP, UA, TPMT, and TB test	None First 2 months: CBC 2/month and CMP monthly Months 2-4: CBC and CMP monthly Month 5+: CBC and CMP q3 months	Total body skin exam for patients on azathioprine >2 years	Nausea and dizziness Bone marrow suppression, GI upset, and hepatitis
Corticosteroids ⁶⁶	BP, glucose if diabetic	Every 3 months: BP, weight, and glucose Yearly: DEXA and lipid profile	Monitor for symptoms of adrenal insufficiency, particularly when receiving systemic corticosteroids >2 consecutive weeks or >3 cumulative weeks in the past 6 months	Adrenal suppression, osteoporosis, weight gain, hyperglycemia, cardiovascular disease, dyslipidemia, cataracts, and glaucoma Growth suppression in children
Cyclosporine (Neoral) ²⁸	BP, CBC, CMP, Mg, uric acid,	Months 1-2: BP, CBC, CMP, Mg, uric acid, lipid panel every 2 weeks Months 3+: BP, CBC, CMP, Mg, uric acid, lipid panel monthly ¹³	Contraindicated in: Uncontrolled hypertension, renal disease, serious infections, and previous history of malignancy. Avoid in patients with high cumulative dose of previous PUVA phototherapy	Renal dysfunction, hypertension, headaches, paresthesias, dose-related hyperbilirubinemia, gingival hyperplasia, and hypertrichosis
Ginkgo biloba ⁵³	None	None		Mild anticoagulant effect, GI effect, and restlessness
Methotrexate ⁶⁷	CBC, CMP, hepatitis panel, and TB test	Months 1-2: CBC q 2-4 weeks, LFTs monthly, and BUN and Cr q 2-3 months Month 3+: CBC, CMP every 3 months	Prior to initiation: Review alcohol intake, risk of hepatitis B or C, and family history of liver disease. During treatment: Supplementation with folic acid	Bone marrow suppression, stomatitis, nausea, anorexia, hepatotoxicity, pulmonary fibrosis, and fetal loss
Minocycline ⁵⁰	None	None		Photosensitivity and GI distress Less common: hyperpigmentation, vertigo, drug-induced lupus, autoimmune hepatitis, and hypersensitivity reaction
Mycophenolate Mofetil (Cellcept) ²¹	CBC, CMP, LFT	Month 1: CBC, CMP, lipid profile q weekly Months 2 and 3: CBC, CMP, lipid profile q 2 weeks Month 3+ CBC, CMP, LFT q monthly		GI side effects: nausea, abdominal pain, diarrhea Less common: neutropenia, anemia, thrombocytopenia
Ruxolitinib (Jakafi) ⁶⁸	CBC, CMP, lipid profile, hepatitis panel, TB test	Month 1: CBC, CMP, lipid profile Month 2+: CBC, CMP, lipid profile q 3 months	Not recommended in: End-stage renal disease patients Avoid in: Patients with neutropenia, thrombocytopenia, and anemia	Anemia, thrombocytopenia, and infection

(Continues)

Table 1 Continued

Generic Name (Alternative Brand Names)	Baseline Laboratory Studies and Monitoring	Ongoing Monitoring*			Representative Side effects [†]
		Comments			
Tofacitinib (Xeljanz) ^{69,70}	CBC, CMP, lipid profile, hepatitis panel, TB test	Month 1: CBC, CMP, lipid profile Month 2+: CBC, CMP, lipid profile q 3 months	Avoid in: Patients with leukopenia, neutropenia, and anemia	Infection, neutropenia, anemia, and hyperlipidemia	

BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CMP, complete metabolic profile; Cr, creatinine; DEXA, dual-energy x-ray absorptiometry; GI, gastrointestinal; LFTs, liver function tests; Mg, magnesium; TB, tuberculosis; TPMT, thiopurine S-methyltransferase; UA, urinalysis.

*With no firm monitoring guidelines developed for the use of immunosuppressive drugs in vitiligo, laboratory tests are obtained less or more frequently depending on dose alterations, and if rapidly changing laboratory values or borderline toxicities are encountered.

[†]Space precludes listing all potential adverse effects.

Table 2 US Food and Drug Administration pregnancy categories of systemic agents for vitiligo

Category	Description	Systemic Agents
A	Adequate and well-controlled human studies failed to show risk to fetus	None
B	No controlled studies have been conducted in humans; animal studies fail to show risk to the fetus	None
C	Animal studies show a risk to fetus; no adequate human studies. Potential benefits may outweigh the risks	Cyclosporine, ¹⁴ ruxolitinib, ¹⁵ and tofacitinib ¹⁶
D	Human studies show evidence of risk to fetus, but benefits of use in pregnant women may outweigh the risks	Azathioprine, ¹⁴ mycophenolate mofetil, ²¹ minocycline, ¹⁷ ginkgo biloba, ¹⁸ and prednisone ¹⁹
X	Human studies show evidence of risk to fetus; risks clearly outweigh any possible benefits	Methotrexate ¹⁴
Unknown category	No pregnancy rating available	Afamelanotide and alpha-lipoic acid

that is critical for the expression and regulation of IL-2. As such, cyclosporine decreases macrophages and lymphocytes in the skin, preferentially inhibiting T-helper cells, with some activity against cytotoxic T cells (Fig. 1d).²⁸

High levels of CD4⁺ and CD8⁺ lymphocytes and low levels of regulatory T cells are present in the dermal-epidermal junction of vitiligo lesions. Higher levels of Type-1 cytokines, tumor necrosis factor- α , IL-8, IFN- γ , CD11c⁺ myeloid dendritic dermal cells, and CD207⁺ Langerhans cells have also been demonstrated in vitiligo lesions, which cyclosporine downregulates.²⁹

Application

Six patients with vitiligo received oral cyclosporine (6 mg/kg/day) for 5 to 30 weeks. One patient demonstrated a minimal to moderate response, and the remaining five demonstrated little or no response.³⁰ Taneja et al. conducted a 12-week, open label study of 18 patients with progressive vitiligo who were treated with oral cyclosporine (3 mg/kg/day). Progressive vitiligo was defined as the development or extension of lesions within

the last 3 months. The progression of vitiligo was halted in 11 of 18 (61%) patients and of these, nine showed repigmentation.³¹

Metha et al. compared the efficacy of cyclosporine with oral dexamethasone mini pulse in patients with active vitiligo. Group 1 received 2.5 mg dexamethasone on 2 consecutive days a week for 4 months, and group 2 received cyclosporine at 3 mg/kg/day. Arrest of disease progression defined as change in vitiligo disease activity score from 4+ to 3+ was significantly lower in group 2 versus group 1 (10.92 weeks vs 13.90 week, P =0.01).³² Other parameters including the extent of repigmentation, improvement in patient assessment score, and vitiligo quality of life were similar between the groups.³²

Side effects

Cyclosporine-induced renal failure is usually duration and dose dependent. Other side effects include hypertension, increased potential of malignancy, neurological and gastrointestinal side effects, and gingival hyperplasia (Table 1).³³

JAK Inhibitors

Ruxolitinib

Mechanism of action

Vitiligo and alopecia areata are interferon (IFN)- γ -driven diseases. IFN- γ binding to its receptor activates the Janus kinase (JAK)-STAT pathway, leading to C-X-C motif chemokine 10 secretion in the skin, which is required for the progression of vitiligo in a mouse model.³⁴⁻³⁶ Ruxolitinib exerts its effects by inhibiting JAK1/2, which is critical for the IFN- γ pathway (Fig. 1e).

Application

A male patient with alopecia areata and vitiligo taking 20 mg of oral ruxolitinib twice daily noted 51% facial repigmentation at week 20, in addition to other areas. Hair growth on the scalp and other vitiliginous patches also occurred.³⁷ Ruxolitinib also has utility in its topical preparation. Rothstein et al. studied 1.5% ruxolitinib cream twice daily in 12 subjects with nonsegmental vitiligo and at least 1% BSA. The average change in Vitiligo Area Scoring Index (VASI) score over 20 weeks in the nine remaining subjects was 27%. Greater efficacy was noted on the face with a VASI score of 76% ($P = 0.001$).³⁸ A recent, randomized double-blinded study of topical ruxolitinib conducted by Rosmarin et al. compared several different formulations and regimens with a control group to assess endpoint of VASI with 50% improvement. One hundred and fifty-seven patients were randomized to several treatment groups (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% daily) and control. The endpoint of VASI 50 was achieved by 45% of the 1.5% twice daily group and 50% in the 1.5% once daily group as compared to only 3% in the control group.³⁹ A further subanalysis revealed that among the 33 patients who received ruxolitinib 1.5% cream BID, a greater proportion of patients were ≥ 50 (58.8% vs 31.3%) and female patients (60.0% vs. 33.3%) responded at week 24 based on the facial VASI 50.⁴⁰ Other characteristics noted with improved response include $\leq 1.5\%$ affected facial BSA at baseline, disease duration >20 years, and previous treatment with phototherapy. For BSA $\leq 20\%$ at baseline using ruxolitinib 1.5% cream BID, the total VASI 50 was greater in the head/neck region (60%), upper extremities (52.9%), and lower extremities (52.6%).⁴⁰ Further clinical trials investigating the efficacy of topical ruxolitinib are currently underway.⁴¹

Side effects

Common side effects include anemia and thrombocytopenia (Table 1).⁴²

Tofacitinib citrate

Mechanism of Action

Tofacitinib citrate acts through inhibition of JAK1/3. As IFN- γ signal transduction occurs through JAK1/2, the use of a JAK1/3

inhibitor could partially block IFN- γ signaling and downstream CXCL10 expression due to JAK 1 inhibition, although likely less effective than JAK1/2.⁴³ Furthermore, interleukin (IL)-15, which signals through JAK1/3, was reported to play a role in disease maintenance by promoting resident memory T cells within vitiligo lesions.⁴⁴ This is another potential mechanism for tofacitinib. IL-15 inhibition, which leads to a reduction in memory T cells, is currently being studied for the treatment of vitiligo (Fig. 1e).⁴⁴

Application

A case report of a patient with 10% BSA, receiving oral tofacitinib, increased to a max dose of 5 mg daily noted 50% repigmentation after 5 months.⁴³ In a case series with 10 patients on 5 to 10 mg of tofacitinib daily or twice daily, five patients achieved an average of a 5.4% decrease in BSA involvement over an average of 9.9 months. The other five patients did not experience repigmentation, perhaps due to a lack of light exposure.⁴⁵ At Henry Ford Hospital, four patients with generalized vitiligo were started on a similar regimen without phototherapy and had no significant repigmentation. No published trials using topical tofacitinib are currently available. However, both topical tofacitinib and ruxolitinib can be prescribed through compounding pharmacies.

Side effects

Side effects include herpes zoster reactivation, upper respiratory tract infections, headaches, and nausea (Table 1).⁴⁶

Antibiotics

Minocycline

Mechanism of action

Minocycline is an antibiotic with antioxidant activity and the ability to attenuate H₂O₂-induced apoptosis of melanocytes *in vitro*, as hydrogen peroxide (H₂O₂) concentrations may decrease melanocyte viability in a concentration-dependent manner. Pretreatment with minocycline in mouse melanocytes also reverses H₂O₂-mediated impairment of melanin synthesis, likely increasing melanocyte viability (Fig. 1f).⁴⁷

Application

Parsad and Kanwar prescribed 100 mg minocycline daily to 32 patients with gradually progressive vitiligo for 3 months. Twenty-nine patients achieved disease stability, and three patients had disease progression. Ten patients showed arrest of depigmentation after 4 weeks. Seven patients showed moderate to marked repigmentation.⁴⁸

In a randomized controlled study, Singh et al. compared the efficacy of dexamethasone OMP therapy versus oral minocycline in patients with active vitiligo. Twenty-five patients received 2.5 mg dexamethasone on 2 consecutive days, and

25 patients received 100 mg minocycline daily. Six (24%) patients in the minocycline and three (12%) patients in the OMP group developed new lesions, an insignificant difference over the 6-month course. They concluded that both are effective for disease stabilization.⁴⁹ However, such “non-inferiority studies” as this one may be underpowered, making it difficult to draw conclusions. Based on these trials and our clinical experience, minocycline has more utility in disease stabilization than repigmentation.

Side effects

Common side effects include photosensitivity and gastrointestinal distress (Table 1).⁵⁰

Antioxidants

Alpha-lipoic acid

Mechanism of action

Alpha-lipoic acid acts as a fatty-acid peroxy and hydroxyl radical scavenger, lipoxygenase inhibitor, and glutathione synthesis promoter. It is also involved in recycling vitamins C and E.⁵¹ These properties may be protective against oxidative stress and halt disease progression, making alpha-lipoic acid useful in combination therapy (Fig. 1g).

Application

Dell’Anna et al. conducted a double-blinded, placebo-controlled trial evaluating the efficacy of NBUVB and antioxidant pool (AP) versus NBUVB alone for generalized vitiligo. The AP contained alpha-lipoic acid (50 mg), vitamin C (50 mg), vitamin E (20 mg), polyunsaturated fatty acids (12%), and cysteine monohydrate (50 mg). Patients (AP; $n = 17$, placebo; $n = 11$) took two tablets of AP or placebo daily for 8 weeks followed by a 6-month period of twice weekly NBUVB with oral medication. Treatment response was evaluated through visual grading of photographs and biochemical parameters of redox status at baseline, 2 and 6 months. After 2 months of AP, catalase activity and reactive oxygen species production were 121% and 57% of base values ($P < 0.05$ and $P < 0.02$ vs placebo, respectively). In the AP group, 47% of patients obtained > 75% repigmentation vs 18% in the placebo group ($P < 0.05$) after 6 months.⁵¹

Li et al. evaluated a combination treatment with oral alpha-lipoic acid, betamethasone injection, and NBUVB in 50 patients with nonsegmental progressive vitiligo. Patients were divided into treatment and control groups and were respectively treated with oral alpha-lipoic acid and placebo, in combination with betamethasone injection and NBUVB. At 3 and 6 months, 40% and 90% of patients in the treatment group achieved > 50% improvement, respectively. The treatment group had better efficacy than control at 3 months, whereas no difference was observed at 6 months.⁵²

Side effects

Nausea and dizziness have been reported (Table 1).⁵³

Ginkgo biloba extract

Mechanism of action

Vitiligo patients have impaired intracellular redox status and depleted antioxidant levels leading to oxidative stress and melanocyte injury. Ginkgo biloba extracts (GBEs) have anti-inflammatory, immunomodulatory, and antioxidant properties. They may attenuate oxidative stress in macrophages and endothelial cells, scavenge superoxide-free radicals, and have effects against ultraviolet B-induced cytotoxicity (Fig. 1h).⁵⁴

Application

In a double-blinded, placebo-controlled trial, Parsad et al. evaluated the efficacy of GBE in patients with limited and slow-spreading vitiligo. Over 6 months, patients in group A ($n = 22$) received GBE 40 mg three times daily, while patients in group B ($n = 22$) received placebo. Patients in group A had a statistically significant halt in disease progression ($P = 0.006$). Marked to complete repigmentation was observed in 10 patients in group A and two patients in group B.⁵⁴

Szczurko et al. conducted a prospective open-label trial in 11 participants, 12 to 35 years old, with 60 mg GBE twice a day for 12 weeks. Results showed a significant improvement in total VASI and Vitiligo European Task Force scores.⁵⁵

Based on these trials and our clinical experience, oral antioxidants such as ginkgo biloba and ALA have more utility in disease stabilization than repigmentation when used in combination with other therapies. Other antioxidants, such as polypodium leucotomos extract, have shown some utility in treating vitiligo, whereas others, such as pseudocatalase, have shown mixed results.⁵⁶⁻⁶²

Side effects

GBE is well tolerated and safe at doses of 120 mg/day (Table 1).⁵³

Hormone analog

Afamelanotide

Mechanism of action

Afamelanotide is an analog of α -melanocyte-stimulating hormone (α -MSH), which stimulates melanocyte proliferation and melanogenesis with protective and anti-inflammatory properties. Melanocortin system defects occur in vitiligo, including low-plasma α -MSH levels, decreased lesional α -MSH levels, and reduced expression of prohormone convertases (Fig. 1i).⁶³

Application

Lim et al. evaluated the efficacy of an afamelanotide implant with narrowband ultraviolet B (NBUVB) phototherapy for generalized vitiligo involving 15% to 50% of BSA with Fitzpatrick skin

phototypes III to VI. Patients were randomized to combination therapy ($n = 28$) versus NBUVB monotherapy ($n = 27$). After 1 month of NBUVB monotherapy, the combination therapy group received 16 mg afamelanotide subcutaneously monthly for 4 months. The combination therapy group had superior repigmentation (represented by a relative reduction in VASI) at 48.64% (95% CI, 39.49%-57.80%) at day 168 vs 33.26% (95% CI, 24.18%-42.33%) in the NBUVB monotherapy group. The combination group also had faster repigmentation (face, 42.0 vs 61.0 days [$P = 0.001$]; upper extremities, 46.0 vs 69.0 days [$P = 0.003$]) with a more noticeable response in patients with Fitzpatrick skin phototypes IV to VI.⁶⁴

Side effects

Notable adverse events include hyperpigmentation and nausea (Table 1).⁶⁴

Clinical experience

In our clinical practice, oral corticosteroids are first-line agents for unstable vitiligo, with minocycline being used for those in whom oral corticosteroids are contraindicated. Steroid sparing agents, especially mycophenolate mofetil, have shown promising results. However, further studies need to be performed. We reserve these agents for patients with a contraindication to oral corticosteroids or minocycline.

We have been using compounded topical tofacitinib and ruxolitinib in clinic for patients who have failed topical steroids and calcineurin inhibitors. Although topical ruxolitinib has more evidence behind its use, it is also more expensive, which can be a limiting factor. In our experience, oral JAK inhibitors in combination with phototherapy are more effective compared to JAK inhibitors alone.

Oral antioxidants, such as alpha-lipoic acid and ginkgo biloba are used in conjunction with other treatments for disease stabilization, rather than repigmentation. They are not used as monotherapy. Polypodium leucotomos, specifically heliocare, is another antioxidant that we have used increasingly due to its consistent product quality.

Afamelanotide continues to be an experimental therapy that has potential for use in vitiligo. However, it is not currently available for use in this indication.

Conclusion

Systemic therapies may benefit patients with unstable, widespread, or recalcitrant vitiligo. However, it is important to recognize their limitations as some agents lack evidence to support their use, with wide variability in outcome measures. These treatments can also be associated with poor efficacy and side effects. Additional barriers include adherence, lack of insurance coverage, and the need for regular laboratory monitoring and appointments.⁶⁵

Some systemic agents that show promise, such as the JAK inhibitors and IL-15 inhibitors, are being studied for broader use. Further studies on systemic agents in vitiligo are necessary, especially as they are a promising therapeutic option for patients who suffer from this difficult to treat condition.

Multiple choice questions (answers provided after references)

- For rapidly progressive vitiligo, which of the following options is the best choice?
 - Ginkgo biloba
 - Minocycline
 - Oral corticosteroids
 - Phototherapy
 - Tofacitinib
- Which of the following options is pregnancy category X?
 - Methotrexate
 - Minocycline
 - Azathioprine
 - Oral corticosteroids
 - Cyclosporine
- Which of the following medications has also shown benefit in alopecia areata?
 - Alpha-lipoic acid
 - Minocycline
 - Ruxolitinib
 - Ginkgo biloba extract
 - Afamelanotide
- Which of the following treatment options do not require laboratory monitoring?
 - Phototherapy
 - Cyclosporine
 - Azathioprine
 - Methotrexate
 - Mycophenolate mofetil
- Which of the following medications is being studied as a topical treatment for vitiligo?
 - Methotrexate
 - Minocycline
 - Cyclosporine
 - Ruxolitinib
 - Afamelanotide
- Dosing of ginkgo biloba extract is 200 mg/day.
 - True
 - False
- Cyclosporine is contraindicated in patients with uncontrolled hypertension.
 - True
 - False

- 8 Folic acid is recommended in conjunction with what other oral medication?
- Oral corticosteroids
 - Minocycline
 - Azathioprine
 - Methotrexate
 - Afamelanotide
- 9 Which of the following oral medications is associated with increased risk of nonmelanoma skin cancers, especially after 1 year of use?
- Methotrexate
 - Oral corticosteroids
 - Azathioprine
 - Minocycline
 - Afamelanotide
- 10 Among the studies noted, the most frequently used medication to compare treatment efficacy are oral corticosteroids.
- True
 - False

Conflict of interest

HWL has received research grants from Incyte, L'Oréal Pfizer, PCORI. He has served as a consultant for Pierre Fabre, ISDIN, Ferndale, La Roche-Posay, Beiersdorf, and as a speaker for La Roche-Posay and Cantabria Labs. J.E.H. is a consultant and investigator for Pfizer, Genzyme/Sanofi, Aclaris Therapeutics, Rheos Medicines, Sun Pharmaceuticals, Villarís Therapeutics, TeVido BioDevices, and EMD Serono. He is a consultant for AbbVie, Janssen, 3rd Rock Ventures, The Expert Institute, and Biologics MD. He is an investigator for Celgene, Incyte, and Dermira. He has equity in TeVido Biodevices, Rheos, and Villarís Therapeutics and is the founder of Villarís Therapeutics. I.H.H. is an investigator for Clinuvel, L'Oreal, Estee Lauder, Ferndale Laboratories, Inc., Pfizer, Bayer, Unigen, Allergan, Johnson & Johnson, Abbvie and Incyte. He is a consultant for Incyte, AbbVie, and Pfizer and is the Global Vitiligo Foundation Co-Chair. T.F.M is an investigator for Avita, Arcutis, Incyte, the National Institute of Allergy and Infectious Diseases, Estee Lauder, Ferndale Laboratories, Inc., and Allergan. T.A., S.F., and M.A.R. have no conflict to disclose.

References

- Harris JE. Immunopathogenesis. In: Hamzavi IH, Mahmoud BH, Isedeh PN, eds. *Handbook of Vitiligo: Basic Science and Clinical Management*. JP Medical Ltd, London: 2016:21–36.
- Ezzedine K *et al.* Vitiligo is not a cosmetic disease. *J Am Acad Dermatol* 2015; **73**(5): 883–885.
- Sharma CK *et al.* Different advanced therapeutic approaches to treat vitiligo. *J Environ Pathol Toxicol Oncol* 2015; **34**(4): 321–334.
- Walling HW, Swick BL. Update on the management of chronic eczema: new approaches and emerging treatment options. *Clin Cosmet Investig Dermatol* 2010; **3**: 99–117.
- Lahiri K, Chatterjee M, Sarkar R. *Pigmentary disorders: a comprehensive compendium*. Jaypee Brothers Medical Publishers (P) Ltd, New Delhi: 2014.
- Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. *Int J Dermatol* 1993; **32**(10): 753–757.
- Radakovic-Fijan S *et al.* Oral dexamethasone pulse treatment for vitiligo. *J Am Acad Dermatol* 2001; **44**(5): 814–817.
- Kanwar AJ, Mahajan R, Parsad D. Low-dose oral mini-pulse dexamethasone therapy in progressive unstable vitiligo. *J Cutan Med Surg* 2013; **17**(4): 259–268.
- Kim SM, Lee HS, Hann SK. The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. *Int J Dermatol* 1999; **38**(7): 546–550.
- Tiede I *et al.* CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest* 2003; **111**(8): 1133–1145.
- Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *J Dermatolog Treat* 2006; **17**(3): 151–153.
- Patra S *et al.* A randomized comparative study of the effect of betamethasone oral mini-pulse therapy versus oral azathioprine in progressive non-segmental vitiligo. *J Am Acad Dermatol* 2021; **85**(3): 728–729.
- Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55**(3): 369–389.
- Kim SC, Hernandez-Diaz S. Editorial: Safety of immunosuppressive drugs in pregnant women with systemic inflammatory diseases. *Arthritis Rheumatol* 2014; **66**(2): 246–249.
- US Food and Drug Administration Prescribing information: JAKAFI (ruxolitinib) (Reference ID: 4546367). 2020 [cited 2020 21 October]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202192Orig1s019Rplbl.pdf.
- US Food and Drug Administration Prescribing information: XELJANZ (tofacitinib) (Reference ID: 4269956). 2018 [cited 2020 21 October]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018l1bl.pdf.
- IBM Corporation. Minocycline hydrochloride. *Micromedex*: IBM Corporation, Armonk, NY: 2020.
- IBM Corporation. Ginkgo biloba. *Micromedex*: IBM, Armonk, NY: 2020.
- US Food and Drug Administration Prescribing information: RAYOS (prednisone) (Reference ID: 3165107). 2012 [cited 2020 21 October]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000l1bl.pdf.
- Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus* 2005; **14**(Suppl 1): s2–s8.
- Orvis AK *et al.* Mycophenolate mofetil in dermatology. *J Am Acad Dermatol* 2009; **60**(2): 183–199. quiz 200-2.
- Bishnoi A *et al.* Oral mycophenolate mofetil as a stabilizing treatment for progressive non-segmental vitiligo: results from a prospective, randomized, investigator-blinded pilot study. *Arch Dermatol Res* 2021; **313**(5): 357–365.
- Singh H *et al.* A randomized comparative study of oral corticosteroid minipulse and low-dose oral methotrexate in the treatment of unstable vitiligo. *Dermatology* 2015; **231**(3): 286–290.
- Cutolo M *et al.* Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. *Ann Rheum Dis* 2001; **60**(8): 729–735.
- Alghamdi K, Khurram H. Methotrexate for the treatment of generalized vitiligo. *Saudi Pharm J* 2013; **21**(4): 423–424.

- 26 Sandra A, Pai S, Shenoj SD. Unstable vitiligo responding to methotrexate. *Indian J Dermatol Venereol Leprol* 1998; **64**(6): 309.
- 27 West J, Ogston S, Foerster J. Safety and efficacy of methotrexate in psoriasis: a meta-analysis of published trials. *PLoS One* 2016; **11**(5): e0153740.
- 28 Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol* 2010; **63**(6): 925–946. quiz 947-8.
- 29 Tarle RG *et al.* Vitiligo--part 1. *An Bras Dermatol* 2014; **89**(3): 461–470.
- 30 Gupta AK *et al.* Oral cyclosporine in the treatment of inflammatory and noninflammatory dermatoses. A clinical and immunopathologic analysis. *Arch Dermatol* 1990; **126**(3): 339–350.
- 31 Taneja A *et al.* Cyclosporine in treatment of progressive vitiligo: An open-label, single-arm interventional study. *Indian J Dermatol Venereol Leprol* 2019; **85**(5): 528–531.
- 32 Mehta H *et al.* Oral cyclosporine is effective in stabilizing active vitiligo: Results of a randomized controlled trial. *Dermatol Ther* 2021; **34**: e15033.
- 33 Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol* 2010; **63**(6): 949–972. quiz 973-4.
- 34 Rashighi M *et al.* CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med* 2014; **6**(223): 223ra23.
- 35 Rashighi M, Harris JE. Serum chemokines herald disease activity and treatment response in vitiligo patients. *Br J Dermatol* 2016; **174**(6): 1190–1191.
- 36 Richmond JM *et al.* Keratinocyte-derived chemokines orchestrate T-cell positioning in the epidermis during vitiligo and may serve as biomarkers of disease. *J Invest Dermatol* 2017; **137**(2): 350–358.
- 37 Harris JE *et al.* Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol* 2016; **74**(2): 370–371.
- 38 Rothstein B *et al.* Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol* 2017; **76**(6): 1054–1060 e1.
- 39 Rosmarin D *et al.* Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet* 2020; **396**(10244): 110–120.
- 40 Hamzavi I *et al.* Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: descriptive subgroup analyses from a phase 2, randomized, double-blind trial. *J Am Acad Dermatol* 2021; **S0190-9622**(21): 01043–01044.
- 41 Incyte Corporation. A study of INCB018424 phosphate cream in subjects with vitiligo (NCT03099304). 2017 [cited 2020 October 22]; Available from: <https://clinicaltrials.gov/ct2/show/NCT03099304>.
- 42 Ho PJ *et al.* Practical management of myelofibrosis with ruxolitinib. *Intern Med J* 2015; **45**(12): 1221–1230.
- 43 Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. *JAMA Dermatol* 2015; **151**(10): 1110–1112.
- 44 Richmond JM *et al.* Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci Transl Med* 2018; **10**(450): eaam7710.
- 45 Liu LY *et al.* Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol* 2017; **77**(4): 675–682 e1.
- 46 Hsu L, Armstrong AW. JAK inhibitors: treatment efficacy and safety profile in patients with psoriasis. *J Immunol Res* 2014; **2014**: 283617.
- 47 Song X *et al.* Minocycline protects melanocytes against H2O2-induced cell death via JNK and p38 MAPK pathways. *Int J Mol Med* 2008; **22**(1): 9–16.
- 48 Parsad D, Kanwar A. Oral minocycline in the treatment of vitiligo--a preliminary study. *Dermatol Ther* 2010; **23**(3): 305–307.
- 49 Singh A *et al.* Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy versus oral minocycline in patients with active vitiligo vulgaris. *Indian J Dermatol Venereol Leprol* 2014; **80**(1): 29–35.
- 50 Garner SE *et al.* Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev* 2012; **2012**(8): CD002086.
- 51 Dell'Anna ML *et al.* Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. *Clin Exp Dermatol* 2007; **32**(6): 631–636.
- 52 Li L *et al.* Triple-combination treatment with oral alpha-lipoic acid, betamethasone injection, and NB-UVB for non-segmental progressive vitiligo. *J Cosmet Laser Ther* 2016; **18**(3): 182–185.
- 53 Gianfaldoni S *et al.* Herbal compounds for the treatment of vitiligo: a review. *Open Access Maced J Med Sci* 2018; **6**(1): 203–207.
- 54 Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol* 2003; **28**(3): 285–287.
- 55 Szczurko O *et al.* Ginkgo biloba for the treatment of vitiligo vulgaris: an open label pilot clinical trial. *BMC Complement Altern Med* 2011; **11**: 21.
- 56 Reyes E *et al.* Systemic immunomodulatory effects of *Polypodium leucotomos* as an adjuvant to PUVA therapy in generalized vitiligo: A pilot study. *J Dermatol Sci* 2006; **41**(3): 213–216.
- 57 Middelkamp-Hup MA *et al.* Treatment of vitiligo vulgaris with narrow-band UVB and oral *Polypodium leucotomos* extract: a randomized double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol* 2007; **21**(7): 942–950.
- 58 Pacifico A *et al.* NB-UVB plus oral *Polypodium leucotomos* extract display higher efficacy than NB-UVB alone in patients with vitiligo. *Dermatol Ther* 2021; **34**(2): e14776.
- 59 Bakis-Petsoglou S, Le Guay JL, Wittal R. A randomized, double-blinded, placebo-controlled trial of pseudocatalase cream and narrowband ultraviolet B in the treatment of vitiligo. *Br J Dermatol* 2009; **161**(4): 910–917.
- 60 Naini FF *et al.* The effect of pseudocatalase/superoxide dismutase in the treatment of vitiligo: a pilot study. *J Res Pharm Pract* 2012; **1**(2): 77–80.
- 61 Schallreuter KU *et al.* From basic research to the bedside: efficacy of topical treatment with pseudocatalase PC-KUS in 71 children with vitiligo. *Int J Dermatol* 2008; **47**(7): 743–753.
- 62 Alshiyab DM *et al.* Comparison of the efficacy of Tacrolimus 0.1% ointment and Tacrolimus 0.1% plus topical pseudocatalase/superoxide dismutase gel in children with limited vitiligo: a randomized controlled trial. *J Dermatolog Treat* 2020; **31**: 1–4.
- 63 Grimes PE *et al.* The efficacy of afamelanotide and narrowband UV-B phototherapy for repigmentation of vitiligo. *JAMA Dermatol* 2013; **149**(1): 68–73.
- 64 Lim HW *et al.* Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. *JAMA Dermatol* 2015; **151**(1): 42–50.
- 65 Constantiner M, Cukor D. Barriers to immunosuppressive medication adherence in high-risk adult renal transplant recipients. *Dialysis and Transplantation* 2011; **40**(2): 60–66.

- 66 Liu D *et al.* A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013; **9**(1): 30.
- 67 Menter A *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009; **61**(3): 451–485.
- 68 Mesa RA, Cortes J. Optimizing management of ruxolitinib in patients with myelofibrosis: the need for individualized dosing. *J Hematol Oncol* 2013; **6**: 79.
- 69 Madan V, Griffiths CE. Systemic ciclosporin and tacrolimus in dermatology. *Dermatol Ther* 2007; **20**(4): 239–250.
- 70 Fellner, C. Pharmaceutical approval update. *P T.* P t, 2016; **41**(4): 220–221.

Answer key

1. C
2. A
3. C
4. A
5. D
6. B
7. A
8. D
9. C
10. A