Brief Summary of Prescribing Information for TREMFYA™ (guselkumab)
TREMFYA™ (guselkumab) injection, for subcutaneous use
See package insert for full Prescribing Information.

INDICATIONS AND USAGE TREMFYA™ is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS Infections:** TREMFYA may increase the risk of infection. In clinical trials, infections occurred in 23% of subjects in the TREMFYA group versus 21% of subjects in the placebo group through 16 weeks of treatment. Upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections occurred more frequently in the TREMFYA group than in the placebo group *[see Adverse Reactions]*. The rate of serious infections for the TREMFYA group and the placebo group was ≤ 0.2%. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing TREMFYA. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TREMFYA until the infection resolves. **Pre-treatment Evaluation for Tuberculosis:** Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA. Initiate treatment of latent TB prior to administering TREMFYA. In clinical studies, 105 subjects with latent TB who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop active TB (during the mean follow-up of 43 weeks). Monitor patients for signs and symptoms of active TB during and after TREMFYA treatment. Consider anti-TB therapy prior to initiating TREMFYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer TREMFYA to patients with active TB infection. **Immunizations:** Prior to initiating therapy with TREMFYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA. No data are available on the response to live or inactive vaccines. **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of labeling: • Infections *[see Warnings and Precautions]* **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In clinical trials, a total of 1748 subjects with moderate-to-severe plaque psoriasis received TREMFYA. Of these, 1393 subjects were exposed to TREMFYA for at least 6 months and 728 subjects were exposed for at least 1 year. Data from two placebo- and active-controlled trials (VOYAGE 1 and VOYAGE 2) in 1441 subjects (mean age 44 years; 70% males; 82% white) were pooled to evaluate the safety of TREMFYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 8 weeks). Weeks 0 to 16: In the 16-week placebo-controlled period of the pooled clinical trials (VOYAGE 1 and VOYAGE 2), adverse events occurred in 49% of subjects in the TREMFYA group compared to 47% of subjects in the placebo group and 49% of subjects in the U.S. licensed adalimumab group. Serious adverse events occurred in 1.9% of the TREMFYA group (6.3 events per 100 subject-years of follow-up) compared to 1.4% of the placebo group (4.7 events per 100 subject-years of follow-up), and in 2.6% of U.S. licensed adalimumab group (9.9 events per 100 subject-years of follow-up). Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA group than in the placebo group during the 16-week placebo-controlled period.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects through Week 16 in VOYAGE 1 and VOYAGE 2

	TREMFYA[a] 100 mg N=823 n (%)	Adalimumab[b] N=196 n (%)	Placebo N=422 n (%)
Upper respiratory infections[c]	118 (14.3)	21 (10.7)	54 (12.8)
Headache[d]	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions[e]	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis[f]	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections[g]	9 (1.1)	0	0
Herpes simplex infections[h]	9 (1.1)	0	2 (0.5)

[a] subjects receiving 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter. [b] U.S. licensed adalimumab [c] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI. [d] Headache includes headache and tension headache. [e] Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria. [f] Gastroenteritis includes gastroenteritis and viral gastroenteritis. [g] Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections. [h] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the TREMFYA group and at a higher rate than in the placebo group through Week 16 in VOYAGE 1 and VOYAGE 2 were migraine, candida infections, and urticaria. Specific Adverse Reactions: *Infections:* Infections occurred in 23% of the TREMFYA group compared to 21% of the placebo group. The most common (≥ 1%) infections were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of TREMFYA. *Elevated Liver Enzymes:* Elevated liver enzymes were reported more frequently in the TREMFYA group (2.6%) than in the placebo group (1.9%). Of the 21 subjects who were reported to have elevated liver enzymes in the TREMFYA group, all events except one were mild to moderate in severity and none of the events led to discontinuation of TREMFYA. Safety through Week 48: Through Week 48, no new adverse reactions were identified with TREMFYA use and the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment. **Immunogenicity:** As with all therapeutic proteins, there is the potential for immunogenicity with TREMFYA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to guselkumab with the incidences of antibodies to other products may be misleading. Up to Week 52, approximately 6% of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing antibodies. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subject who experienced loss of efficacy after developing high antibody titers. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions. **DRUG INTERACTIONS Live Vaccinations:** Avoid use of live vaccines in patients treated with TREMFYA *[see Warnings and Precautions]*. **CYP450 Substrates:** The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation. Results from an exploratory drug-drug interaction study in subjects with moderate-to-severe psoriasis suggested a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 but the interaction potential cannot be ruled out for drugs metabolized by CYP2D6. However, the results were highly variable because of the limited number of subjects in the study. Upon initiation of TREMFYA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **USE IN SPECIFIC POPULATIONS Pregnancy:** Risk Summary: There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, TREMFYA may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 30 times the maximum recommended human dose (MRHD). Neonatal deaths were observed at 6- to 30-times the MRHD *(see Data)*. The clinical significance of these nonclinical findings is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data: *Animal Data:* In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age. **Lactation:** Risk Summary: There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA and any potential adverse effects on the breastfed infant from TREMFYA or from the underlying maternal condition. **Pediatric Use:** The safety and efficacy of TREMFYA in pediatric patients (less than 18 years of age) have not been established. **Geriatric Use:** Of the 1748 subjects with plaque psoriasis exposed to TREMFYA, a total of 93 subjects were 65 years or older, and 4 subjects were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger subjects who received TREMFYA. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **OVERDOSAGE** In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately. **PATIENT COUNSELING INFORMATION** Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before starting TREMFYA therapy, and each time the prescription is renewed, as there may be new information they need to know. Infections: Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*. Instruction on Injection Technique: Instruct the patient or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique. Instruct patients who are self-administering to inject the full dose of TREMFYA *[see Medication Guide and Instructions for Use]*. Instruct patients or caregivers in the technique of proper needle and syringe disposal. Needles and syringes should be disposed of in a puncture-resistant container. Advise patients and caregivers not to reuse needles or syringes. Remind patients if they forget to take their dose of TREMFYA to inject their dose as soon as they remember. They should then take their next dose at the appropriate scheduled time.

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Papulosis linfomatoide

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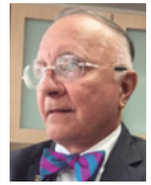

Carlos Sarriera Lazaro, MD

Introducción

La papulosis linfomatoide es una erupción cutánea caracterizada por pápulas y nódulos recurrentes que sanan por sí mismos. Tiene un curso crónico que puede durar meses o años.

A nivel histológico, hay células T atípicas con proliferación linfoide CD30+ que podrían confundirse con un linfoma maligno. El pronóstico de la condición es excelente, aunque se ha visto que estos pacientes tienen un riesgo aumentado de desarrollar un linfoma maligno.

Epidemiologia y patogénesis

La papulosis linfomatoide es una condición rara (en los Estados Unidos se estima entre 1,2 y 1,9 casos por millón de personas), puede ocurrir a cualquier edad, con mayor incidencia después de los 50 años. Entre un 5 y un 50% se puede relacionar con un linfoma maligno. Su etiología aún se desconoce, pero se asocia a una sobreexpresión de CD30 en las células T atípicas que resulta en su proliferación, ocasionando las lesiones características. Una hipótesis es que la eventual regresión de estas lesiones se debe a un mecanismo de apoptosis aumentado en estas células atípicas.

Presentación clínica

Las lesiones clásicas de la papulosis linfomatoide son pápulas y nódulos eritematosos o violáceos, que luego desarrollan una hemorragia central, necrosis y costra (Figura 1). Estas coexisten en diferentes estadios de desarrollo y son clínicamente indistinguibles de las lesiones del linfoma anaplásico de células grandes.

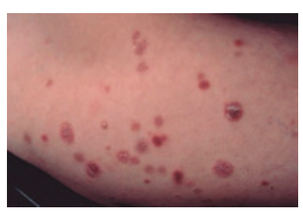

Figura: Papulosis linfomatoide. Pápulas y nódulos eritematosos y violáceos en diferentes estadios de desarrollo, algunos con hemorragia central, necrosis y costra asociada.

Después, desaparecen espontáneamente en un periodo de 2 a 8 semanas. Su curso es crónico y recurrente y puede durar hasta más de 40 años. Las lesiones no ocurren en ningún lugar en particular, pero usualmente se encuentran en las extremidades, manos, cara y genitales. Raramente aparecen en las membranas mucosas.

Diagnóstico

Clínicamente, se debe sospechar la papulosis linfomatoide en aquellos pacientes que presentan una erupción de lesiones papulares y nodulares recurrentes, en diferentes estadios de desarrollo y que sanan espontáneamente en ausencia de síntomas constitucionales. Para confirmar el diagnóstico, es necesaria una biopsia de piel. Se recomienda que se haga una excisión completa de 2 o más de las lesiones inflamatorias que no demuestren evidencia de necrosis o involución.

Histológicamente, la papulosis linfomatoide varía de acuerdo con el estadio de la lesión. Se ha reportado que existen 6 tipos histológicos mayores de esta condición, siendo el tipo A el más común (representa el 75% de los casos). Se caracteriza por un infiltrado denso, superficial y profundo dermal (perivascular e intersticial) en forma de cuña de células T atípicas entremezcladas con linfocitos pequeños, neutrófilos, eosinófilos e histiocitos. Se pueden apreciar varias mitosis que podrían ser atípicas. El patrón histológico tipo A es muy similar al infiltrado polimórfico del linfoma de Hodgkin. Un análisis inmunohistoquímico revela la expresión de CD30 y otros antígenos relacionados al linfoma de Hodgkin en estas células T atípicas grandes. La evaluación molecular demuestra un reordenamiento clonal de genes TCR en 40 a 100% de los casos de papulosis linfomatoide.

Hacer el diagnóstico de papulosis linfomatoide puede ser difícil, ya que la histología es altamente variable dependiendo al estadio de la lesión y puede solapar –al igual que la presentación clínica– la apariencia del

linfoma anaplásico de células grandes. Es por esto por lo que es indispensable llevar a cabo una correlación clinicopatológica cuando se sospecha esta condición, para así llegar a un diagnóstico certero y establecer un plan de tratamiento adecuado.

Diagnóstico diferencial

El diagnóstico diferencial de papulosis linfomatoide incluye: linfoma cutáneo primario anaplásico de células grandes, micosis fungoide, pitiriasis liquenoide y varioliforme aguda (PLEVA), pitiriasis liquenoide crónica (PLC), foliculitis, granuloma de Majocchi, picada de artrópodo y sarna.

Tratamiento

Existen varias modalidades de tratamiento para la papulosis linfomatoide que pueden acelerar la resolución de las lesiones existentes y prevenir el desarrollo de nuevas. Sin embargo, ninguna terapia altera el curso natural de la condición ni previene el desarrollo de un linfoma asociado.

Para pacientes con enfermedad limitada, se puede usar esteroides tópicos súper-potentes. Para pacientes con enfermedad extensa y sintomática, se sugiere usar metotrexato oral o subcutáneo en dosis baja (5 a 35 mg por semana) con ácido fólico oral (1 mg diario) como terapia inicial. El metotrexato es un tratamiento efectivo para suprimir la condición. Sin embargo, al dejar de tomarlo, la misma recurre en un periodo de 1 a 2 semanas.

En aquellos pacientes que no respondan a metotrexato o con una contraindicación al mismo, se recomienda terapia con psoraleno oral con radiación ultravioleta A (PUVA) 2 veces por semana por 6 a 8 semanas o hasta que se vayan las lesiones. Para pacientes pediátricos con enfermedad extensa, se recomienda el uso de esteroides tópicos o fototerapia con radiación ultravioleta B de banda estrecha (UVB). Existe evidencia limitada de otros posibles tratamientos para esta condición, tales como terapia fotodinámica, retinoides orales o tópicos, carmustina tópica, entre otros, que han demostrado tener algún efecto de supresión de la condición en estudios pequeños o en reportes de caso.

Linfomas asociados

En estudios recientes, se ha visto que más del 50% de los pacientes con papulosis linfomatoide desarrollan un linfoma maligno antes, durante o después de tener la condición. Los linfomas más comunes son micosis fungoide, linfoma anaplásico cutáneo o nodal de células grandes y linfoma de Hodgkin. No se han establecido criterios o hallazgos particulares que puedan predecir la progresión de papulosis linfomatoide a un linfoma maligno. Por esto, es muy importante que el médico evalúe a su paciente por lo menos 2 veces al año y que lo instruya a evaluarse si comienza a padecer de fiebre, escalofríos, sudoración nocturna, malestar general o pérdida de peso, si le salen lesiones papulares o nodulares que no se resuelven por sí solas en menos de 2 meses o si se percatan de nódulos linfáticos agrandados en el cuello, área inguinal o en las axilas.

Comentario

La papulosis linfomatoide se puede confundir clínica-mente e histológicamente con otras entidades benignas y malignas de la piel. Es por esto que es esencial hacer una correlación clínica completa cuando se sospeche esta condición para confirmar el diagnóstico, tratar al paciente con prontitud y vigilar que la enfermedad no progrese a una malignidad.

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