administered dose, taking it daily instead of weekly,[6] which is what happened in our case.

Use extreme caution when prescribing MTX, especially in elderly patients, and careful prescription, not only verbally but also in writing, of the dose to be administered weekly as well as insisting on these to both the patients and the relatives and primary care professionals, are needed in order to avoid serious complications.

References

1. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68:1100–4.
2. Preet Singh Y, Aggarwal A, Misra R, Agarwal V. Low-dose methotrexate-induced pancytopenia. Clin Rheumatol. 2007;26:84–7.
3. Lim AY, Gaffney K, Scott DG. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. Rheumatology (Oxford). 2005;44:1051–5.
4. Gutiérrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum. 1996;39:272–6.
5. Sáenz D, Ruiz FJ, Monón S, Mozota J, Marquina A. Neumonitis secundaria a metotrexate. An Med Interna. 2008;25:27–30.
6. Metotrexato por vía oral: reacciones adversas graves derivadas de la confusión en la dosis administrada. Agencia Española del Medicamento y Productos Sanitarios. MUH (FV); 2011. Available from: http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2011/NI-MUH_11-2011.htm [accessed 11.11.11].

Lorena Expósito Pérez,* Juan José Bethencourt Baute, Sagrario Bustabad Reyes

Servicio de Reumatología, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

* Corresponding author.
E-mail address: Lorena_lep@hotmail.com (L. Expósito Pérez).

Triple therapy with non-biologic DMARDs for rheumatoid arthritis or biologic therapy. Is it the same?

Triple terapia con FARME no biológico o tratamiento biológico para artritis reumatoide. ¿Son lo mismo?

The goals for rheumatoid arthritis (RA)—remission or low disease activity— are achieved through combination therapy with disease-modifying antirheumatic drugs (DMARDs) or biologic therapy. DMARDs combination therapy achieve the goals in higher percentage than DMARD monotherapy[1,2]. Recently O'Dell et al. compared triple therapy with three non-biologic DMARDs, and biologic therapy with etanercept-methotrexate in RA[3]. This comparison is important for developing countries because the poor availability through social security[4].

O'Dell and colleagues did not find significant differences in DAS28 (using erythrocyte sedimentation ratio, ESR or C reactive protein, CRP). Even DAS28 is considered the "gold standard" for evaluating disease activity, other clinical measures such as ultrasound or MRI might improve sensitivity for the targets in RA patients[5–8]. The study reported that patients receiving biologic therapy achieved American College of Rheumatology ACR50 and ACR70 almost 10% higher than triple therapy. Previous studies informed improved productivity of daily work8 and slow or not radiographic progression in patients under biologics therapy, although the significance related with the structural differences is not clinically defined[1,9,10]. It is clear that there are benefits for patients receiving biologic therapy.

The clinical benefits of triple therapy previously mentioned are relevant in most RA patients when compared to efficacy of DMARD combination. This is especially an attractive treatment because of the lower cost of triple therapy compared to biologics, particularly in developing countries. Although we do not have official data related with social security in México, approximately 20% of RA patients covered by ISSSTE (11% of total Mexican population), and less than 5% of IMSS (59% of total Mexican population) are receiving a biological therapy; Mexican population with no social security is a rare event to prescribe biologic therapy. However, although triple therapy can be more accessible than biologics, the latter treatment becomes necessary for at least in 20-30% of RA patients particularly when individual treatment is refractory to methotrexate. Nonetheless, treatments with higher doses of methotrexate[11,12], in combination with prednisone[13] or with another combination of DMARD, reduces the percentage of patients requiring biologics therapy[1,14,15]. We suggest that initial triple DMARDs therapy for RA as the first therapy for monotherapy non-responsive patients and biologics must be reserved for refractory triple DMARDs therapy.

Bibliografía

1. Rantalaiho V, Kautiainen H, Korpela M, Hannonen P, Kaipiainen-Seppänen O, Möttönen T, et al., for the NEO-RACo Study Group. Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomised clinical trial, the NEO-RACo trial. Ann Rheum Dis. 2013, doi: 10.1136/annrheumdis-2013-203497.[Epub ahead of print].
2. Boers M, van Tuy L, van den Broek M, Kostense PJ, Allaart CF. Meta-analysis suggests that intensive non-biological combination therapy with step-down prednisolone (COBRA strategy) may also disconnect' disease activity and damage in rheumatoid arthritis. Ann Rheum Dis. 2013;72:406–9.
3. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S14–36.
4. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369:307–18.
5. Burgos-Vargas R, Catoggio LJ, Galarza-Maldonado C, Ostojich K, Cardiel MH. Current therapies in rheumatoid arthritis: a Latin American perspective. Reumatol Clin. 2013;9:106–24.
6. Martínez-Martínez MU, Cuevas-Orta E, Reyes-Vaca G, Baranda L, González-Amaro R, Abud-Mendoza C. Magnetic resonance imaging in patients with rheumatoid arthritis with complete remission treated with disease-modifying antirheumatic drugs or anti-tumour necrosis factor alpha agents. Ann Rheum Dis. 2007;66:134–5.
7. Hernández-Núñez E, Cuevas-Orta E, Santillán-Guerrero E, Moreno-Valdés R, Sánchez-Arriaga A, Ávila-Sánchez JA, et al. Remisión sostenida en pacientes con artritis reumatoide agresiva. Estudio comparativo de abatacept y pacientes con 3 ó más fármacos modificadores de la enfermedad. Reumatol Clin. 2011; 7 Supl.:C1-CM022.
8. Sakellariou G, Scirè CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis. 2013;72:245–9.
9. Furuya H, Kasama T, Isozaki T, Umemura M, Otsuka K, Isojima S, et al. Effect of TNF antagonists on the productivity of daily work of patients with rheumatoid arthritis. J Multidiscip Healthc. 2013;6:25–30.

10. Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2014, doi: 10.1136/annrheumdis-2013-204577. [Epub ahead of print].
11. Dhillon S. Intravenous Tocilizumab: A Review of Its Use in Adults with Rheumatoid Arthritis. BioDrugs. 2013 [Epub ahead of print].
12. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose escalation of parenteral methotrexate in active rheumatoid arthritis that has been unresponsive to conventional doses of methotrexate: a randomized, controlled trial. Arthritis Rheum. 2004;50:364–71.
13. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literatura. Ann Rheum Dis. 2009;68:1094–9.
14. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al., on behalf of the Utrecht Rheumatoid Arthritis Cohort Study Group. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis. A randomized trial. Ann Intern Med. 2012;156:329–39.
15. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis. 2012;72:72–8.

Carlos Abud-Mendoza * Marco U. Martínez-Martínez

Unidad Regional de Reumatología y Osteoporosis, Hospital Central "Dr. Ignacio Morones Prieto" y Facultad de Medicina de la Universidad Autónoma de San Luis Potosí, San Luis Potosí, S.L.P., México

* Autor para correspondencia.
E-mail address: c_abud@hotmail.com (C. Abud-Mendoza).

Cryptococcal Meningoencephalitis in a Patient With Rheumatoid Arthritis Treated With Methotrexate and Prednisone☆

Meningoencefalitis criptococócica en una paciente con artritis reumatoide tratada con metotrexato y prednisona

To the Editor:

Cryptoccoccus neoformans is an encapsulated biotrophic fungus that is transmitted as an aerosol.[1] Its origin has been identified in *Eucalyptus camaldulensis*, its infective forms are basidiospores and encapsulated yeast, and its vector is dried bird droppings, especially from pigeons.[1] Cryptococcal infections were commonly found in immunocompromised persons with alterations in cellular immunity.[2] Since the introduction of highly active antiretroviral therapy (HAART), the incidence of these infections has decreased dramatically due to better virological and immunological control, due to the decrease in viral load and increase in CD42 cell count. Cryptococcal infections have been reported in patients with a history of prolonged use of corticosteroids, diabetes, renal disease, immunosuppressive therapy, solid organ transplant, lymphoma, sarcoidosis and idiopathic lymphopenia CD42. The cases of cryptococcal infection in patients with rheumatoid arthritis (RA) are limited to a few papers, and when reviewing the literature there are only 3 reported cases of cryptococcal meningitis as the admission diagnosis. We report the case of a young patient with RA, who was not undergoing biological therapy and presented a meningoencephalic syndrome. The patient is a 49-year-old woman with a history of RA for the past 5 years, treated with methotrexate 15 mg weekly and prednisone 15 mg/day; she came to the emergency department due to having suffered 4 days of intense occipital headache, progressive, incoherent speech, disorientation, with memory problems, drowsiness, and in the last 24 h, fever. Upon neurological examination she was markedly confused, with impaired memory, judgment and altered calculus and ocular tenderness. Laboratory tests showed: ESR: 63 mm/h; CRP 8.3 mg/dl; glucose 353 mg/dl, sodium 134 mg/dl. It was initially considered as a meningoencephalic syndrome. Lumbar puncture was performed, with an opening pressure of 31 cm H_2O, low glucose

Table 1
Cryptococcal Infections Reported in Patients With Rheumatoid Arthritis.

Age/Gender	Site of infection	Treatment	Comorbidity/Outcome	Reference
65/M	Pulmonary	MTX, HXQ, Infl	No/recovery	Shrestha et al. (2004)
44/M	Pulmonary	Pred, MTX, Lefl, Infl	No/recovery	Starrett et al. (2002)
69/M	Pulmonary	Pred, MTX, Infl	DM2/recovery	True et al. (2002)
47/F	Pulmonary	Pred, Infl	No/recovery	Arend et al. (2004)
61/M	Pulmonary	Pred, MTX, Lefl, Infl	No/recovery	Hage et al. (2003)
67/F	Meninges	Pred, MTX, Infl	No/recovery	Muñoz et al. (2007)
82/F	Pulmonary/ meninges	Pred	?/Death	Tajiri et al. (2009)
80/M	Leather/disseminated	MTX, Pred	ERC/death	Diaz et al. (2010)
74/M	Skin	Pred	DM2/recovery	Moosbrugger et al. (2008)
58/F	Skin	MTX, HXQ, Adal	Trauma	Morgan et al. (2008)
49/F	Brain-meninges	MTX, Pred	DM2 *de novo*/treatment	Threshing et al. (2012)
70/M	Brain-meninges	Infl, Ritux, Pred, MTX	None	Wingfield et al. (2011)
Average age: 63.8	Pulmonary: 50% Skin: 16% Meninges: 16% Disseminated: 8.3%	MTX: 75%; Pred: Infl 75%: 50%; Lefl: HXQ 16%: 16%; Adal: Biological 8.3%: 66%	DM2: 16%; ERC: 8.3%	Percentage of patients according to variables

Adal: adalimumab; DM2: type 2 diabetes mellitus; F: female; HXQ: hydroxychloroquine; Infl: infliximab; Lefl: leflunomide; M: male; MTX: methotrexate; Pred: prednisolone; Ritux: rituximab.
Source: based on Muñoz et al. (2007).[7]

☆ Please cite this article as: Trillos RF, Fernández-Ávila DG, Díaz MC, Gutiérrez JM. Meningoencefalitis criptococócica en una paciente con artritis reumatoide tratada con metotrexato y prednisona. Reumatol Clin. 2014;10:346–347.