

Eficacia del infliximab en espondiloartropatías refractarias. Resultados de la experiencia europea

Grupos de interés en el Estudio de las Espondiloartropatías:
Español, Francés, Belga y Alemán

LA EXPERIENCIA ESPAÑOLA. GRUPO ESPAÑOL DE INTERÉS EN EL ESTUDIO DE LAS ESPONDILOARTROPATÍAS*

En la actualidad disponemos de los datos correspondientes a los 22 primeros pacientes con espondiloartropatía activa y refractaria a terapias habituales (AINE, FAME) según criterios definidos previamente por nuestro grupo de trabajo, que han concluido el estudio a 30 semanas. El esquema terapéutico consistió en 3 dosis de carga 0,2 y 6 semanas con 5 mg/kg para seguir con una infusión cada 8 semanas de forma similar a los pacientes con AR. La administración concomitante de metotrexato no se contemplaba en estos pacientes (los resultados previos se han comunicado en los resúmenes del Congreso Nacional de la Sociedad Española de Reumatología (SER 2001) y al Congreso Internacional de la European League Against Rheumatism (EULAR 2001).

	BASDAI (M ± DE)	BASFI (M ± DE)	Global (VAS) ^a (M ± DE)	VSG (M ± DE)	PCR (mg/l) (M ± DE)
Semana 0	73 ± 14	72 ± 14	81 ± 13	42 ± 30	36 ± 30
Semana 2	43 ± 23	No evaluado	53 ± 25	14 ± 13	4,6 ± 3,8
Semana 6	40 ± 24	42 ± 24	47 ± 25	12 ± 11	5,8 ± 5,5
Semana 14	40 ± 21	49 ± 24	53 ± 21	15 ± 14	11,4 ± 10,6
Semana 22	42 ± 25	No evaluado	42 ± 29	22 ± 21	16,8 ± 12,7
Semana 30	44 ± 24	57 ± 26	57 ± 28	17 ± 15	10,5 ± 10,2
p (Semana 0 frente a 30)	0,000	0,019	0,003	0,001	0,011

*Escala

Conclusiones

1. La dosis empleada de 5 mg/kg de peso parece adecuada para el tratamiento de estos pacientes.
2. El intervalo entre infusiones durante la fase de mantenimiento (cada 8 semanas) parece adecuado, aunque se precisan estudios longitudinales mayores para establecer su duración.

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3. La mejoría se observa desde la primera dosis.
4. La respuesta clínica y analítica es francamente satisfactoria.

5. En general, el fármaco es bien tolerado.

No obstante, quedan aún algunas cuestiones por dilucidar que precisarán estudios más amplios. Entre ellas, destacamos los siguientes interrogantes:

1. ¿Durante cuánto tiempo debe seguirse administrando el fármaco para seguir manteniendo una respuesta clínica satisfactoria?
2. ¿Cuál es la pauta de administración más idónea, en la fase de mantenimiento de la respuesta?
3. ¿Pueden aparecer más efectos adversos al prolongarse la administración del fármaco?

THE FRENCH EXPERIENCE. RESULTS OF A 6 MONTHS FOLLOW-UP OPEN-LABEL STUDY

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We enrolled 50 patients (38 M/12 F; mean age = 36 ± 9 yr; 87% HLA-B27+). 47 (94%) completed the treatment, as scheduled, whereas 1 and 2 received only 1 and 2 infusions, respectively. Altogether, 49 patients (94%) were responders, as defined by ASAS criteria. Maximum improvement was observed at week 8 for most parameters, as is shown in table.

Characteristic	Baseline	Week 8	Variation (%)	p value
Disease activity (VAS) ^a	70 ± 2.9	19 ± 3.1	-71%	< 0.0001
Global pain (VAS)	67 ± 3.1	18 ± 3.1	-72%	< 0.0001
BASDAI	58 ± 2.2	17 ± 2.3	-72%	< 0.0001
BASFI	61 ± 3.0	19 ± 3.0	-69%	< 0.0001
CRP (mg/L)	49 ± 4.3	7 ± 1.6	-76%	< 0.0001

^aVisual analogue score 0 to 100 mm.

Relapse defined by a loss of ≥ 50% of global pain improvement was observed in 96% of completers within 4 months after the last infusion, with an average delay of 7 weeks (range: 2-18 weeks).

Conclusion

Most patients suffering of inflammatory active AS promptly and dramatically respond to treatment with infliximab. A majority of responders experience relapse within 4 months of drug discontinuation.

THE BELGIAN EXPERIENCE

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Infliximab was first given in 4 patients with Crohn's disease who also presented peripheral arthritis or axial involvement; a significant decrease of articular as well as axial inflammation, together with a resolution of gut symptoms was found in all these patients.

Based on these data, an open-label study in 21 patients suffering from long-standing therapy resistant spondyloarthropathies, (including different subgroups of SpA) was started. After a loading dose of 3 infusions of infliximab (5 mg/kg) at week 0, 2 and 6, patients were treated every 14 weeks, resulting from day 3 on in a statistical improvement of all measured parameters (global disease activity, peripheral arthritis, axial disease) and maintained during 84 days (3 months), without important side-effects.

In a double-blind placebo-controlled study of 40 patients with SpA, a highly statistical significant improvement of all clinical and biological variables in the infliximab treated group was found during the 20 weeks treatment. However, in this group in one treated patient a severe drug-related adverse event appeared: a form of disseminated tuberculosis.

The patients of the first open-label study were followed for one year to determine whether repeated infusions would effectively and safely maintain the observed effect. By giving repeated infusions, a sustained significant decrease of all disease manifestations was observed.

Before retreatment, recurrence of symptoms was observed in 16% of the patients at week 20, 68% at week 34 and 79% at week 48, indicating that an interval of 14 weeks is too long to obtain an adequate disease control; however, no loss of efficacy was observed after retreatment. During this follow-up 12 patients (57%) developed antinuclear antibodies and 4 of them developed double-stranded DNA antibodies, however without lupus-like symptoms.

Conclusions

These data indicate that blockade of TNF- α is highly effective in reducing signs and symptoms in

different forms of SpA, suggesting that for the first time, there may be an effective therapeutic option for all disease manifestations of severe SpA. However, the recurrence of tuberculosis observed in 1 patient, necessitates strict inclusion criteria. Moreover, long term experience and follow-up is needed to determine the optimal maintenance regimen (dose and interval) and to detect possible long term side-effects.

THE GERMAN EXPERIENCE

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There is now overwhelming evidence that infliximab is effective in the short-term treatment of severe active AS. In a randomized controlled multicenter trial performed in Germany with 70 AS patients over 3 months, 50% improvement of BASDAI was the primary outcome parameter: infliximab was significantly more effective than placebo in more than half of the patients. These strongly positive results have been reproduced in many countries in open studies. Several patients with undifferentiated spondyloarthritis, a possible early form of AS, have been successfully treated with infliximab. There is clearly reason to think that infliximab therapy of AS is a milestone in the treatment of severe AS.

However, there are still questions to be answered. There is hope but we do not know how long the effects last and whether we can prevent progression to ankylosis. Our own preliminary results using MRI suggest that this is indeed the case. The optimal dose is not known yet. In the vast majority of the studies 5 mg/kg have been used but 3 mg/kg may well work in patients as well. Individual dosing might finally turn out to be superior to treat individual patients. There are first studies suggesting that etanercept is also effective to treat AS patients.

The effects of infliximab treatment of the synovium and the immune system have been examined by the Belgian colleagues from Gent. There are indications that the synovial inflammation is effectively suppressed and that the ability to secrete cytokines is reinstituted.

There are rare but significant undesired effects of anti-TNF treatment.

Tuberculosis, allergic reactions and lupus-like disease have occurred in single patients. As it stands now, the impressive positive effects for the patients which are mostly felt as early as one day after the initiation of therapy, seem to clearly outweigh these shortcomings. However, caution must be taken with this effective treatment and cooperation with experienced rheumatologic centers to monitor therapy is strongly recommended.

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