No relevant escalation in dosage of infliximab or other biologic agents over 12 months of treatment – Results from the German Biologic Register

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Reports from Sweden and the USA show dose increase in a considerable number of patients treated with infliximab. We investigated which dosage regimen is used in routine care in Germany and how frequently dose increase or decrease occurs over 12 months in patients treated with the various biologics.

Patients and methods

Since May 2001, patients with RA with a new prescription of etanercept (ETA), infliximab (INF), anakinra (ANAK, since 01/2003) or adalimumab (since 09/2003) and control patients have been consecutively enrolled in 191 rheumatology practices and clinics in Germany. Follow-up has been performed after 3, 6 and 12 months. Patients who were enrolled up to 08/2003 and followed up until 09/2004 have been included in this analysis.

Table 1: Patient characteristics at baseline

Patients enrolled up to August 2003	Etanercept	Infliximab	Anakinra
N	511	346	70
Age in years, mean (SD)	53.7 (12.6)	53.6 (12.6)	54.3 (11.6)
Women (%)	78.1	70.8	77.1
Duration of disease in years, median (IQR)	9.0 (5.0 – 16.5)	8.0 (4.0 – 14.0)	13.0 (7.0 – 22.0)
Rheumatoid factor positive (%)	80.8	78.9	77.1
DAS28, mean (SD)	6.1 (1.2)	6.0 (1.2)	6.1 (1.2)
FFbH (% of full function; mean (SD))	52.7 (23.4)	53.9 (21.7)	52.2 (24.2)
HAQ, mean (SD) *	1.7 (0.7)	1.7 (0.6)	1.7 (0.7)
No. of previous DMARDs, mean (SD)	3.7 (1.5)	3.6 (1.6)	4.2 (1.9)

* HAQ was calculated from the FFbH scores using HAQ = 3.16 – 0.028 x FFbH

Results

In Germany, the recommended dosage of ETA is 25 mg twice a week, of ANAK 100 mg/d and of INF 3 mg/kg body weight every 8 weeks after a loading dose at weeks 0, 2, and 6. As INF comes in vials of 100 mg, exact dosing is difficult, and in routine care the dose is rounded up or down to whole vials. Dosage can be adjusted to disease activity by changing either the dose of the individual administration or the intervals between treatments.
Table 2 shows the doses of INF per administration, after 3 and 12 months. Mean dose per administration hardly changed in this period (3.2 to 3.3 mg/kg). However, the intervals were shorter than 8 weeks in 29% of the cases after 3 months and in 27% after 12 months; the intervals were longer in 6% after 12 months.

Taking both dose and time interval into account, the total mean dose per administration per 8 weeks was 3.8 mg/kg after 3 months and 3.7 mg/kg after a year. In other words, 72% of the patients received a total dose greater than 3.0 mg/kg/8 weeks, and one quarter less.

Table 2: Dosage and administration intervals

Patients enrolled up to August 2003 Completers (after 1 year) N = 223	Infliximab	
	3 months	1 year
Mean dose per administration (mg/kg)	3.2	3.3
Mean dose per 8-week interval (mg/kg)	3.8	3.7
Interval between infusions 8 weeks	71.4%	66.9%
Interval between infusions shorter than 8 weeks	28.6%	27.0%
Interval between infusions longer than 8 weeks	-	6.1%
Mean length of interval (weeks)	7.2	7.5
Dose exactly 3 mg/kg every 8 weeks	5 (2.7)	3 (1.6)
Higher dose	135 (71.8)	138 (72.3)
Lower dose	48 (25.5)	50 (26.2)

Mean doses per administration of ETA and ANAK corresponded to the recommendations and did not change over 12 months. It is of note that in 10% of the patients treated with ETA the intervals between administrations were prolonged. The mean number of administrations per week was 1.9 at 12 months.

Table 3: Improvement in DAS28

DAS28, mean (SD)	N	Baseline	3 months	6 months	1 year
Infliximab, high (> 3 mg/kg)	112	6.3 (1.2)	4.7 (1.7)	4.4 (1.7)	4.6 (1.7)
Infliximab, low (≤ 3 mg/kg)	48	5.8 (1.2)	4.7 (1.5)	4.8 (1.7)	4.8 (1.7)
Etanercept	217	6.2 (1.1)	4.4 (1.5)	4.2 (1.6)	4.2 (1.6)
Anakinra	34	6.2 (1.1)	4.8 (1.6)	4.9 (1.6)	4.8 (1.6)

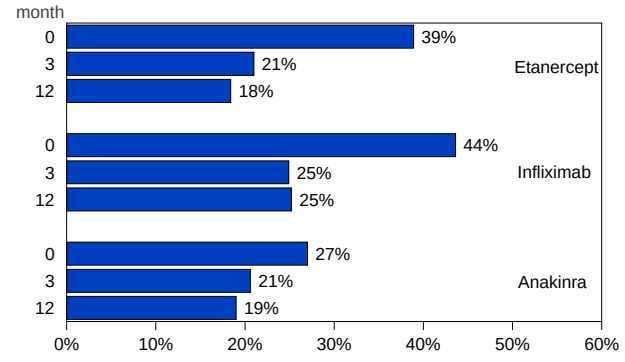
Intention to treat analysis (patients withdrawn from treatment with biologics were included with their last valid value on biologic treatment); only patients newly started on biologics.

In order to analyse whether patients with INF dosages of 3 mg/kg or less might have been insufficiently treated we compared changes in the DAS28 score within the first year of treatment. The figures for ETA and ANAK are given for comparison. Patients who had a dosage of up to 3 mg/kg at 3 months started with a better DAS28 score but showed significantly less improvement than those who started with higher doses.

Glucocorticoids

Concomitant therapy with glucocorticoids was considerably reduced in patients treated with biologics. Especially high-dose glucocorticoids could be reduced significantly.

Figure 1: Patients receiving >7.5 mg glucocorticoids (%)



Conclusion

There was virtually no increase in individual doses of INF or other biologics over the first 12 months of treatment in routine rheumatological care. However, from the loading dose onwards, intervals were shorter than recommended in one quarter of the patients treated with INF. On the other hand, prolongation beyond the recommended treatment interval occurred in 6% of the INF patients and in 10% of those on ETA.

It cannot be ruled out that a proportion of the patients treated with INF did not receive a sufficient dose because German rheumatologists are trying to reduce costs and make do with the lowest acceptable dose. In some patients, this may lead to suboptimal disease control.

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