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Reduced mandibular growth in experimental arthritis in the temporomandibular joint treated with intra-articular corticosteroid

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SUMMARY The aim of this investigation was to study the effect of intra-articular (i.a.) corticosteroid injections (IACIs) in the temporomandibular joint (TMJ) on mandibular development in antigen-induced TMJ arthritis. Ten-week-old female New Zealand white rabbits ($n=42$) were randomly divided into four groups: group A, control (no injections); group B, placebo (repeated i.a. TMJ saline injections); group C, untreated arthritis (repeated induction of TMJ arthritis); and group D, steroid (repeated induction of TMJ arthritis + IACI). All animals had two tantalum implants inserted in the right side of the mandible serving as stable landmarks for later growth analysis. One implant was inserted close to the symphysis and one in the molar region. Computerized tomographic (CT) full-head scans were carried out at 14 (T1) and 26 (T2) weeks of age. (Dropout of animals at T2; group C, $n=7$, and group D, $n=3$.) Absolute and relative intra- and inter-group growth variations were evaluated during the growth period by comparison of CT scans. One-way analysis of variance was used for T1 statistical analysis, and absolute intra-group and relative inter-group growth differences between T1 and T2 were evaluated by Student's *t*-tests.

At T2, the animals in the group A had greater sagittal and vertical mandibular growth compared with the other three groups. TMJ arthritis caused diminished mandibular growth. However, relative mandibular growth was significantly less in group D. The findings of this study do not indicate a positive long-term effect in the use of IACI in the TMJ as an early treatment intervention against TMJ inflammation in growing individuals.

Introduction

Temporomandibular joint (TMJ) involvement in patients with juvenile idiopathic arthritis (JIA) causes destructive changes in the TMJ resulting in significant growth disturbances of the craniomandibular complex (Stabrun, 1991; Rönning *et al.*, 1994; Kjellberg, 1995). The mandibular growth alterations following TMJ involvement in children with JIA are well described (Larheim *et al.*, 1981; Stabrun *et al.*, 1987; Myall *et al.*, 1988; Kjellberg, 1995; Pedersen *et al.*, 2001; Sidiropoulou-Chatzigianni *et al.*, 2001). Skeletal and dentoalveolar JIA growth disturbances primarily affect the mandible resulting in a reduction of posterior face height, retrognathism, increased mandibular inclination and jaw angle, antegonial notching, and an anterior open bite with an increased horizontal overjet. The maxilla is affected by a decrease in vertical development. Orthopaedic and surgical treatment of these growth alterations is often necessary and may lead to acceptable results (Pedersen *et al.*, 1995; Pedersen, 1998). However, such treatments are of long duration, substantial, and complex. It would therefore be beneficial if growth abnormalities could be avoided by early treatment of the initial inflammatory changes in the TMJ. In children, intra-articular (i.a.) corticosteroid injections (IACI) are widely used to reduce inflammation in joints other than the TMJ (Honkanen *et al.*, 1993; Padeh and Passwell, 1998; Eberhard *et al.*, 2004).

In contrast to other joints, the mandibular endochondral growth zone is located i.a. in the cartilage of the mandibular condyles (Copray and Duterloo, 1986; Delatte, 2005), and the concern is whether IACI *per se* may cause growth retardation. No studies have dealt with the effect of repeated IACI in the TMJ on mandibular growth where the aim of treatment is to inhibit inflammatory damage in the TMJ. The anti-inflammatory effect of IACI in experimental arthritis has been demonstrated previously (Küseler *et al.*, 2004) and recently it has been shown that corticosteroid injections in the TMJ in children with JIA reduces pain, inflammation, and improves the function of the TMJ (Arabshahi *et al.*, 2005). Thus, it may be anticipated that a reduction in inflammation in the TMJ may minimize the mandibular growth alterations observed in JIA patients. Consequently, injections should be initiated before irreversible destruction and severe abnormalities occur in the TMJs. The aim of the study was to clarify whether IACI in the TMJ will influence mandibular growth in animals with experimentally induced TMJ arthritis.

Materials and methods

The study was approved by the Danish Ethical Committee for animal welfare. Forty-two, 10-week-old female New Zealand white rabbits housed at the animal facilities of the University of Aarhus, Denmark, with access to food and water *ad libitum*, were used in the study. The welfare was monitored by daily evaluation of food and drink intake.

The animals were randomly divided into four groups and subjected to the procedures shown in Figure 1. The animals in group A ($n=7$) served as the controls and received no treatment or i.a. injections. From the 10th to the 14th week, the animals in groups B ($n=5$), C ($n=15$), and D ($n=15$) were systemically pre-sensitized with ovalbumin (Sigma Chemicals Co., St Louis, Missouri, USA) and incomplete Freunds adjuvant (Sigma Chemicals Co.). In week 14, the animals in groups C and D had arthritis induced in the TMJs according to earlier described methods (Kapila *et al.*, 1995; Tavakkoli-Jou *et al.*, 1999). To maintain chronic arthritis throughout the study, the animals in groups C and D received a total of four 0.1 ml of 10 mg/ml ovalbumin i.a. TMJ injections, with 3-week interval, during the 12 weeks of observation. One week after each reinduction procedure, group D animals received a TMJ injection of 0.1 ml of 20 mg/ml triamcinolone hexacetonide (Lederspan®, Meda, Allerød, Denmark). At each reinduction procedure, group B were injected i.a. with 0.1 ml saline. During the repeated TMJ antigen challenges, 10 animals were lost due to anaphylactic shock (seven in group C and three in group D). At the last reinduction, the ovalbumin concentration was reduced from 10 to 5 mg/ml. No animals were lost at the last reinduction procedure. Arthritis was induced and treated bilaterally.

All animals had two 1.0×0.33 mm tantalum implants inserted in the right side of the mandible serving as landmarks for growth analysis (Björk, 1968; Björk and Skieller, 1977). One implant was inserted close to the symphysis and the other in the molar region. Two computerized tomographic (CT) full-head scans (Philips/Mx8000 IDT 16) were carried out at 14 (T1) and 26 (T2) weeks of age in order to perform intra- and inter-group variation growth analysis.

All surgery was carried out under general anaesthesia. Three millilitres of a mixture of 20 ml ketamine (50 mg/ml),

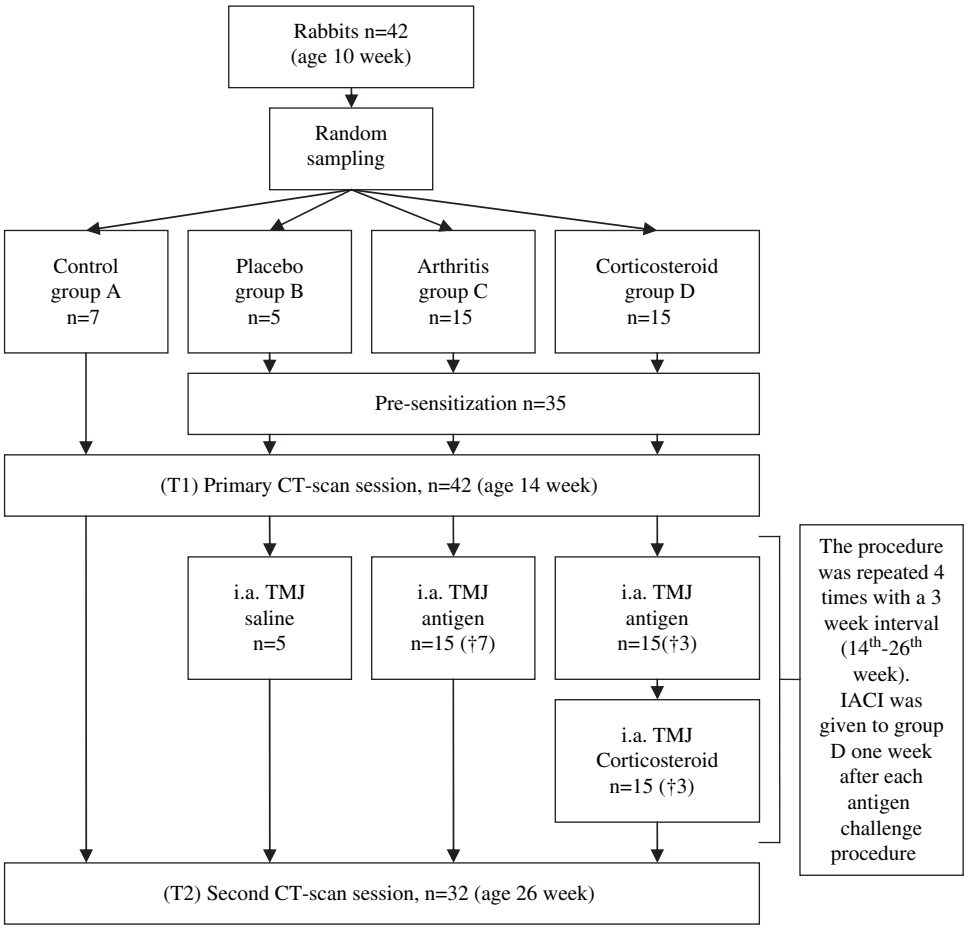

Figure 1 Forty-two, 10-week-old New Zealand white rabbits randomly divided into four groups. † Number of animals lost before the second CT scan session. At T2 (26 week), 32 animals were available for growth analysis.

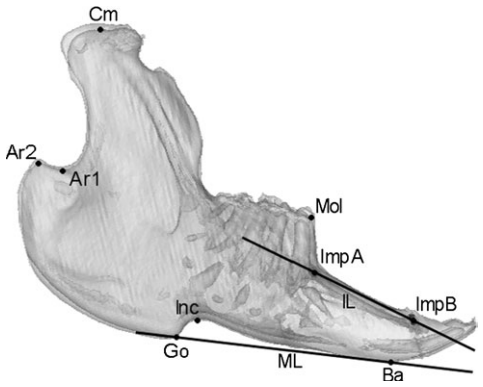

Figure 2 Definition of anatomical landmarks: condylar midpoint (Cm), the midpoint of the condylar head located at the bisection of the absolute sagittal length of the upper margin; articulare 1 (Ar1), the most inferior point on the convex margin located dorsally to the mandibular collum; articulare 2 (Ar2), the most posterior point on the posterior border of the ramus; and gonion (Go), the most inferior and anterior point on the ramus. Basion (Ba), the most inferior point located anteriorly on the lower border of the mandibular body. Incisal point (Inc), the most superior point in the concavity of the lower border of the mandibular body. Molar point (Mol), point located on the mesial cusp tip on the first molar. The implant points were located on the right side: implant A (ImpA), inserted in the posterior mandibular body below and anterior to the molars and the alveolar bone; implant B (ImpB), inserted in the mandibular symphysis, in a dorsal direction to the right incisor. The following two lines were defined: mandibular line (ML), from Go–Ba, defined at the right side; implant line (IL), a line through ImpA–ImpB.

2.5 ml xylazine (20 mg/ml), and 1.0 ml acepromazine (10 mg/ml) were administered to each animal. The animals were killed using 3 ml (200 mg/ml) intravenous pentobarbital under general anaesthesia.

Analysis of the CT scans

Figure 2 shows the anatomical landmarks and implants used for definition of the variables measured on all CT scans. The scanned images were digitized by one author (PS) using the image evaluation software program, Mimics (Version 8.1, Materialise, Leuven, Belgium).

Constructed lines and angles

Figures 2 and 3 show the lines and angles constructed and measured for description of the changes in mandibular morphology.

Prior to the start of this investigation, the decision was made that variables describing vertical and sagittal changes were those from the right side of the animals. Gonion (Go) and the condylar midpoint (Cm) on the left side of each animal were used for transverse measurements.

The relative values for the mandibular dimensional differences between T1 and T2 were obtained using the formula:

$$\frac{(LT2-LT1)\times 100}{LT1},$$

where LT1 is the length or angle of a given variable at T1 (week 14) and LT2 is the length or angle of the same variable at the end of the growth period at T2 (week 26).

Statistical analysis

The data were statistically treated using the software program Stata (Intercooled Stata 8.2, StataCorp, Texas, USA). One-way analysis of variance (ANOVA) tests were used for each variable at T1 and for the relative inter-group differences at T2. Additionally, absolute intra-group growth between T1 and T2 was compared using a paired *t*-test, and the inter-group differences in relative growth using a two-sample *t*-test. A value less than $P=0.05$ was considered significant.

The necessity for a Bonferroni correction for avoidance of mass significance in the post-ANOVA inter-group *t*-tests was evaluated. However, this correction was too strong due to the correlation between the investigated variables (19 variables obtained from each of the 32 animals completing the investigation) and allowed type-1 errors to occur. A post-study power calculation showed sufficient power for the essential findings of this investigation.

Error of the method

Intra-observer variance was determined by repeating measurements of all 19 variables on 10 randomly chosen animal scans. The duplicate measurements were undertaken with a 2-week interval. Ten animals had duplicate scans taken at T1. Statistical analyses were undertaken to determine intra-observer variance and inter-scan accuracy at T1 using Dahlberg's formula (Dahlberg, 1940; Bland and Altman, 1986).

Results

During the study, no difference in daily food intake was observed between the groups. However, at T2 a weight difference was found between groups A and B; the animals in group B were significantly heavier.

The measured variables were all normally distributed. The mean intra-observer variance was 0.3 mm. For all single variables, the error of the method was less than 0.5 mm, except for antegonial notch height (ANH) which was 0.6 mm. All angles showed a method error of less than 0.55 degrees. Statistical analysis of inter-scan accuracy showed an acceptable variance of less than 0.17 mm.

Absolute mean values for the cephalometric measurements of the CT scan at T1 are shown in Table 1. Comparable measurement values were found in all four groups. However at T1, the animals in group D (TMJ arthritis + steroid) had a significantly larger vertical dimension (total posterior and collum mandibular heights) in relation to groups B and C before the start of treatment.

Only small local condylar erosions were observed during the evaluation of the CT scans, and no difficulties were experienced in identifying the condylar midpoint on the T2 CT scans.

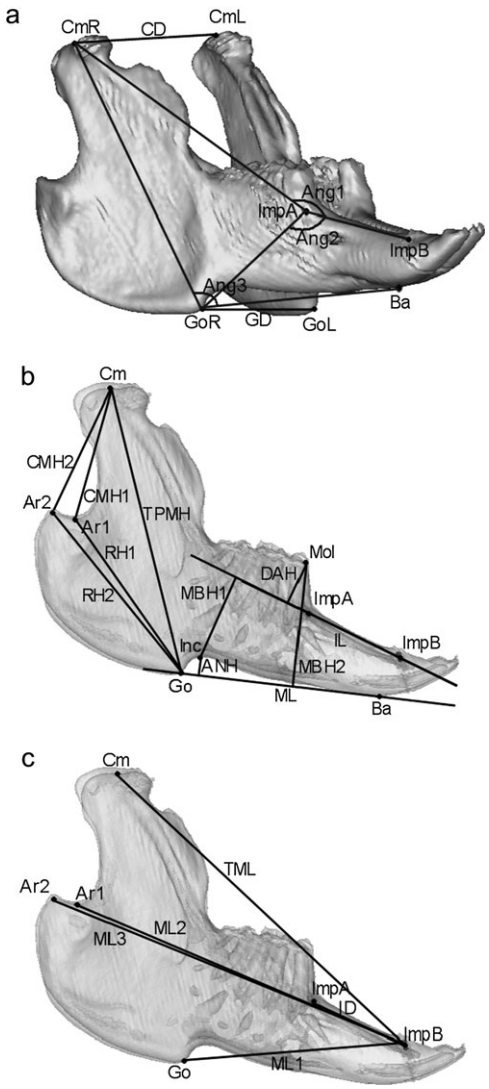

Figure 3 Varibales measured. (a) Transverse—angle 1: Cm–ImpA–ImpB; angle 2: Go–ImpA–ImpB; angle 3: Cm–Go–Ba; condylar distance (CD): $Cm_{(right)}$–$Cm_{(left)}$; gonial distance (GD): $Go_{(right)}$–$Go_{(left)}$. (b) Vertical—total posterior mandible height (TPMH): Cm–Go; collum mandibular height 1 (CMH1): Cm–Ar1; collum mandibular height 2 (CMH2): Cm–Ar2; ramus height 1 (RH1): Ar1–Go; ramus height 2 (RH2): Ar2–Go; mandibular body height 1 (MBH1) Inc ⊥ IL; mandibular body height 2 (MBH2): Mol ⊥ ML; dentoalveolar height (DAH): Mol ⊥ IL; height of the angular notch (ANH): Inc ⊥ ML. (c) Sagittal—mandibular length 1 (ML1): Go–ImpB; mandibular length 2 (ML2): Ar1–ImpB; mandibular length 3 (ML3): Ar2–ImpB; total mandibular length (TML): Cm–ImpB; implant distance (ID): ImpA–ImpB.

Angles

Cm and Go midpoints changed in relation to the implants (Table 2, angles) resulting in significant changes of angles 1 and 2 only in group D between T1 and T2. From T1 to T2, Cm moved posteriorly and Go anteriorly resulting in an increase in angle 1 and a decrease in angle 2 in the group D animals. The mandibular angle (angle 3) opened in groups, B, C, and D (Table 2, angles). No statistical significant inter-group differences were observed between any of the four groups (Table 3).

Vertical changes

The absolute intra-group development of collum mandibular height was significant for all groups during T1 and T2 (Table 2, vertical). There was no absolute vertical development seen in the collum mandibular height from the condyle to articular 1 (Ar1) point in group D. Neither the distance from the molars (mandibular body height 1, MBH1) nor from the incisal point (Inc) (MBH2) changed in relation to the implant line in any of the groups. Dentoalveolar height (DAH) from the molars (Mol) to the mandibular line (ML) increased significantly in all groups. The ANH (Inc ⊥ ML) did not differ except for group D animals where a significant increased notching height was seen (Table 2, vertical).

The relative inter-group differences for vertical total posterior mandibular height (TPMH) were all significantly different from each other except for the comparison of TPMH between groups B and C (Table 3). The largest vertical dimensional increase from T1 to T2 was observed in group A. This was partly confirmed by the change in collum mandibular height (CMH1 and CMH2). The increase in ramus height 1 (RH1) distance from Ar1 to Go was significant between groups A and C ($P<0.05$), C and D ($P<0.05$), and A and D ($P<0.001$). No significant differences were seen in the vertical dimension, in the dentoalveolar area or mandibular body except for the distance from MolR to ML in groups B and D.

Sagittal changes

The absolute mandibular sagittal growth related to implant B increased significantly in all four groups. Both in the condyle [total mandibular length (TML)] and the posterior part of the ramus (ML2 and ML3), significant growth was observed in relation to implant B. Go point moved posteriorly in relation to implant B (ML1) in group A and posteriorly and downwards in group D. There was no change in the inter-implant distance between T1 and T2 (Table 2, sagittal).

TML from the condyle to implant B was less developed in group D compared with the other experimental groups and the controls (Table 3). The ML1 distance from Go to implant B was significantly ($P<0.05$) greater for group A compared with the other groups, where no significant difference was seen. The ML2 and ML3 distances from points Ar1 and Ar2 to implant B were increased significantly more in group A compared with group D. Significance was also seen in the ML2 distance (Ar1-implant B) between groups A and B, where the largest change occurred in group A. The distance between the implants, A and B, did not change in any group.

Transversal changes

The absolute gonial distance (GD) between the right and left Go point increased significantly in groups C and D. The

Table 1 Basic absolute mean values of variables (mm) with a statistical inter-group evaluation of differences between the groups at the start of the experiment at age 14 weeks.

	Control (A)	Placebo (B)	Arthritis (C)	Arthritis + steroid (D)	Significance	ANOVA
TPMH	44.48	43.6	43.62	44.74	D > (B.C)*	*
CMH1	21.52	21.19	20.97	21.92	D > (B.C)*	*
CMH2	22.26	21.63	21.54	22.49	D > (B.C)*	*
RH1	27.37	27.54	27.49	28.05	n.s.	n.s.
RH2	29.87	29.37	29.34	29.77	n.s.	n.s.
MBH1	6.16	6.12	6.18	6.58	n.s.	n.s.
MBH2	2.68	2.35	2.91	2.87	n.s.	n.s.
DAH	18.16	18.1	18.21	18.01	n.s.	n.s.
ANH	12.32	14.79	13.76	13.76	n.s.	n.s.
TML	63.51	62.58	61.99	62.48	n.s.	n.s.
ML1	38.36	37.64	37.16	37.04	n.s.	n.s.
ML2	57.45	57.8	56.89	57.25	n.s.	n.s.
ML3	61.2	59.76	59.24	59.63	n.s.	n.s.
GD	27.42	28.54	27.01	27.72	n.s.	n.s.
CD	33.39	32.53	32.73	33.15	n.s.	n.s.

*$P < 0.05$ (see Figures 1 and 3a–c); n.s., not significant.

distance between the condyles increased during growth in all groups (Table 2, transverse).

Table 3 shows that the increase in intergonial distance was significantly different between groups C and D, with the largest increase in group C.

Discussion

Treatment of craniomandibular growth alterations in children with JIA is mainly focused on the use of functional appliances and symptom relief (Kjellberg, 1995; Pedersen *et al.*, 1995; Pedersen, 1998). The success of treatment is dependent on early diagnosis and interceptive treatment for an acceptable long-term result (Pedersen, 1998). To diagnose TMJ involvement in patients with JIA is difficult since TMJ inflammation may be present without radiographic condylar changes (Küseler *et al.*, 1998). Clinically, it is occasionally observed that moderate mandibular growth disturbances are evident before radiological visible erosions of the condyles are present. In this context, an early pharmaceutical treatment approach may be considered with IACI aiming to prevent the destruction of the condyle and the mandibular growth zone. It is known that corticosteroid injections in the TMJ inhibit local inflammatory changes (Küseler *et al.*, 2004; Arabshahi *et al.*, 2005; Kristensen *et al.*, 2006). This treatment is widely used in other joints in JIA patients (Honkanen *et al.*, 1993; Padeh and Passwell, 1998; Eberhard *et al.*, 2004). However, little is known about the long-term effect of i.a. TMJ corticosteroid injections in JIA patients, and since the endochondral growth zone is located i.a., IACI may result in growth changes.

According to Kapila *et al.* (1995) and Tavakkoli-Jou *et al.* (1999), using the same experimental arthritis model as in the present study, the antigen-induced arthritis model results in a similar impact to the TMJs and mandibular development in rabbits as those seen in JIA children with TMJ involvement. The growth disturbances observed in group C in the present study are analogous to the findings of Tavakkoli-Jou *et al.* (1999) describing growth deviations in rabbits with induced TMJ arthritis.

Restricted mandibular growth was found in group C, and especially in group D in relation to group A. The intra-group changes of the angles in group D suggest a reduction in ramus height growth (angle 1) and a change in the morphology of the area of the sub-angular notch (angle 2). Both of these local mandibular growth deviations are characteristic for human mandibular development in JIA patients with TMJ involvement (Kreiborg *et al.*, 1990; Kjellberg, 1995; Sidiropoulou-Chatzigianni *et al.*, 2001). In group D, the Cm moved posteriorly, and, in relation to the condyle, the DAH increased vertically which caused an opening of angle 1. The fact that TPMH was larger than in groups B and C at T1 only enhances the result. According to Björk (1968), unfavourable growth takes place when the condyle grows in a posterior direction in humans. In group A, angle 1 did not open, as it did in group D, and therefore an unfavourable growth pattern could be the explanation for this rotation in group D. The same conclusion could be drawn in relation to closing of angle 2. Go point moved downward in relation to the incisal point in group D (see Results for the changes in antegonial notching height), indicating an increase of sub-angular notching. This was not observed in groups A, B, or C. An increase of the sub-angular notch is a sign of unfavourable changes in mandibular growth in children with TMJ arthritis (Stabrun, 1991; Kjellberg, 1995). The mandibular angle, angle 3, opened indicating a critical rotation of the mandibular complex in groups B, C, and D compared with group A. The changes of the angles indicating opening of the mandibular angle and an increase of the sub-angular notch are signs of unfavourable growth and similar to those observed in JIA

Table 2 Absolute intra-group differences between T1 (week 14) and T2 (week 26) (see Figure 3a–c).

Variable	Group	T1	T2	Differences between T2 and T1	Difference in SD	Statistical significance
Angles (degrees)						
Angle 1	A	154.33	156.97	2.63	3.6	n.s.
	B	160.07	161.24	1.17	2.9	n.s.
	C	158.14	158.28	0.14	7.1	n.s.
	D	157.19	159.61	2.42	2.3	*
Angle 2	A	142.48	139.19	−3.29	3.9	n.s.
	B	127.49	127.04	−0.45	3.4	n.s.
	C	127.89	130.23	2.34	14.6	n.s.
	D	131.81	130.24	−1.57	1.8	*
Angle 3	A	108.43	109.7	1.2	1.4	n.s.
	B	108.11	111.07	2.96	1.1	*
	C	108.69	110.51	1.82	2.1	*
	D	108.23	110.28	2.05	1.3	*
Vertical (mm)						
TPMH (CmR–GoR)	A	44.48	49.39	4.9	0.5	*
	B	43.6	47.49	3.89	0.2	*
	C	43.62	47.9	4.28	0.5	*
	D	44.74	47.23	2.49	0.9	*
CMH1 (CmR–Ar1)	A	21.52	23.62	2.1	0.6	*
	B	21.19	22.49	1.3	0.3	*
	C	20.97	22.65	1.68	0.6	*
	D	21.92	22.28	0.36	0.8	n.s.
CMH2 (CmR–Ar2)	A	22.26	24.05	1.80	0.7	*
	B	21.63	23.21	1.58	0.3	*
	C	21.54	23.07	1.53	0.5	*
	D	22.49	23.02	0.53	0.6	*
RH1(Ar1–GoR)	A	27.37	30.53	3.15	2.1	*
	B	27.54	29.95	2.41	0.7	*
	C	27.49	30.12	2.63	0.7	*
	D	28.05	30.05	2	0.6	*
RH2 (Ar2–GoR)	A	29.87	33.52	3.65	0.9	*
	B	29.37	32.75	3.38	0.7	*
	C	29.34	32.53	3.19	0.7	*
	D	29.77	32.66	2.89	0.6	*
MBH1 (IncR ⊥ IL)	A	6.16	6.50	0.34	0.8	n.s.
	B	6.12	6.96	0.84	1.4	n.s.
	C	6.18	6.06	−0.12	1.1	n.s.
	D	6.58	6.89	0.31	0.7	n.s.
MBH2 (MolR ⊥ IL)	A	2.68	2.54	−0.14	0.4	n.s.
	B	2.35	2.27	−0.08	0.8	n.s.
	C	2.91	2.81	−0.1	0.6	n.s.
	D	2.87	2.84	−0.03	0.5	n.s.
DAH (MolR ⊥ ML)	A	18.16	19.86	1.7	0.5	*
	B	18.1	19.85	1.75	0.3	*
	C	18.21	19.46	1.25	0.9	*
	D	18.01	19.14	1.13	0.6	*
ANH (IncR ⊥ ML)	A	12.32	14.11	1.79	1.5	n.s.
	B	14.79	16.14	1.34	1.7	n.s.
	C	13.76	14.5	0.74	1.6	n.s.
	D	13.76	14.91	1.15	0.9	*
Sagittal (mm)						
TML (CmR–ImpB)	A	63.51	69.75	6.09	1.2	*
	B	62.58	67.24	4.66	0.7	*
	C	61.99	67.13	5.14	1.7	*
	D	62.48	66.1	3.62	1.1	*
ML1 (GoR–ImpB)	A	38.36	40.79	2.43	1.3	*
	B	37.64	38.41	0.77	0.6	n.s.
	C	37.16	38.22	1.06	1.4	n.s.
	D	37.04	38.32	1.28	0.9	*
ML2 (Ar1–ImpB)	A	57.45	62.51	5.06	2.9	*
	B	57.8	60.4	2.6	0.7	*
	C	56.89	60.21	3.32	1.9	*
	D	57.25	60.04	2.79	1.4	*

Table 2 continued.

Variable	Group	T1	T2	Differences between T2 and T1	Difference in SD	Statistical significance
ML3 (Ar2–ImpB)	A	61.2	66.38	5.23	1.3	*
	B	59.76	63.85	4.09	0.6	*
	C	59.24	63.42	4.18	1.6	*
	D	59.63	63.49	3.86	1.1	*
ID (ImpA–ImpB)	A	13.88	15.07	1.19	1.3	n.s
	B	18.34	18.59	0.25	0.4	n.s.
	C	17.15	17.86	0.71	2.3	n.s.
	D	16.46	16.81	0.35	0.6	n.s.
Transverse (mm)						
GD (GoR–GoL)	A	27.42	29.73	2.31	2.5	n.s.
	B	28.54	29.27	0.73	1.1	n.s.
	C	27.01	28.15	1.14	0.5	*
	D	27.72	28.39	0.67	0.7	*
CD (CmR–CmL)	A	33.39	34.51	1.11	0.6	*
	B	32.53	33.54	1.01	0.7	*
	C	32.73	34.05	1.32	0.8	*
	D	33.15	34.34	1.19	0.8	*

*$P<0.05$; n.s., not significant.

Table 3 Relative inter-group differences in mandibular growth between T1 (week 14) and T2 (week 26).

Group	ANOVA	Post-ANOVA tests					
		Control (A)–placebo (B)	Control (A)–arthritis (C)	Arthritis (C)–steroid (D)	Control (A)–steroid (D)	Placebo (B)–steroid (D)	Placebo (B)–arthritis (C)
Angle 1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Angle 2	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Angle 3	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
TPMH (Cm–Go)	*	*A>B	*A>C	**C>D	**A>D	**B>D	n.s.
CMH1 (Cm–Ar1)	*	*A>B	n.s.	**C>D	**A>D	*B>D	n.s.
CMH2 (Cm–Ar2)	*	n.s.	n.s.	**C>D	*A>D	**B>D	n.s.
RH1 (Ar1–Go)	*	n.s.	*A>C	*C>D	**A>D	n.s.	n.s.
RH2 (Ar2–Go)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
MBH1 (Inc ⊥ IL)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
MBH2 (Mol ⊥ IL)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
DAH (Mol ⊥ ML)	*	n.s.	n.s.	n.s.	n.s.	B>D*	n.s.
ANH (Inc ⊥ ML)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
TML (Cm–ImpB)	*	*A>B	n.s.	C>D*	**A>D	B>D*	n.s.
ML1 (Go–ImpB)	*	*A>B	*A>C	n.s.	*A>D	n.s.	n.s.
ML2 (Ar1–ImpB)	*	*A>B	n.s.	n.s.	*A>D	n.s.	n.s.
ML3 (Ar2–ImpB)	*	n.s.	n.s.	n.s.	*A>D	n.s.	n.s.
ID (ImpA–ImpB)	n.s.	n.s	n.s	n.s	n.s.	n.s.	n.s.
GD (GoR–GoL)	*	n.s.	n.s.	C>D*	n.s.	n.s.	n.s.
CD (CmR–CmL)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

*$P<0.05$, **$P<0.001$; n.s., not significant.

patients. The increase in TML showed growth in all groups. The inter-group differences seen in relative TML were significantly less in group D.

The increase in the mandibular length 1 (ML1) in group A was considered to be a result of a sagittal change since the ANH did not change in this group, indicating an increase in mandibular length. In group D, ML1 also significantly increased. Since the increase in length was larger in group A and as the absolute ANH significantly changed in group D, this finding was interpreted as apposition of bone in the Go area in the group D animals. The change in Go in relation to implant B (ML1) emphasizes the pronounced unfavourable growth pattern seen in the group D animals. In groups B and C, a less pronounced reduction in sagittal growth was observed. Mandibular sagittal length (ML2 and ML3) increased significantly in all groups. However, sagittal growth was reduced in all three experimental groups and most pronounced in group D.

In the vertical dimension, growth was evident in all groups. Collum mandibular height 1 (CMH1) increased with one exception: there was no significant increase from T1 to T2 in group D. For TPMH, group A had the largest increase, while the smallest was seen in group D. It is possible that bone apposition in the sub-angular notch area was responsible for the increase in the TPMH in group D. The measurements for ramus height (RH1) showed almost the same trend. A diminished posterior vertical dimension of the mandible is a typical finding in patients with JIA (Stabrun, 1991; Kjellberg, 1995; Sidiropoulou-Chatzigianni *et al.*, 2001). However, in this study an even more diminished posterior vertical dimension was observed in group D compared with group C.

During growth, no significant changes occurred in the distance from the incisal point to the implant line or in the distance from the implant line to the molar. In relation to the mandibular line, the distance to the molar increased significantly during growth which means that the molar and the dentoalveolar bone gained height in all four groups, indicating that the implant line followed the molars in their eruption and the incisal point likewise followed the implant line.

Normal growth will cause some resorption in the Go area as the condyle lengthens (Enlow and Hans, 1996). No significant change in the distance from the incisal point to the mandibular line (ANH) was observed except for group D indicating remodelling of the sub-angular notch. In group D, ANH increased indicating bone apposition in the area, characteristic of deviant growth forming the sub-angular notch in humans (Kjellberg, 1995). Additionally, growth in the transverse dimension showed a significantly reduced intergonial distance in group D animals compared with group C. This highlights the altered mandibular growth in the Go area in the steroid-treated animals in group D.

The minor non-significant mandibular growth differences between groups A and B suggest an influence of the injections alone on mandibular growth. However, the cause of this influence is unclear since no inflammatory or destructive structural changes were observed histologically in the TMJs after injection with physiological saline (Kristensen *et al.*, 2006).

This is the first investigation describing the effects of IACI in the TMJ on mandibular growth in experimentally induced arthritis. Both *in vitro* and *in vivo* studies of systemic glucocorticoid administrations on the cartilage of the mandibular condyle in newborn mice have shown a wide range of side effects: an inhibitory effect of triamcinolone on DNA synthesis, arrest of cartilage cell proliferation due to triamcinolone administration, and a significant reduction is uptake and incorporation of [3H]thymidine leading to a significant decrease in the number of young cartilage cells, even occurring at relatively low doses of triamcinolone (Silbermann *et al.*, 1977, 1981; Maor and Silbermann, 1986; Weiss *et al.*, 1986, 1988). Emkey *et al.* (1996) concluded that IACI had no net effect on bone resorption and only a transient systemic effect on bone formation in rheumatoid arthritis patients. In contrast, Wenneberg *et al.* (1991) found no skeletal side effects (using panoramic radiography) after monitoring the long-term effect of IACI in the TMJs of adult patients.

The rabbits were 10 weeks old when systemic sensitization was started and 14 weeks old when they had the first i.a. TMJ antigen induction. According to a study on the cranial development of the New Zealand white rabbit (Masoud *et al.*, 1986) approximately 90 per cent of overall mature sagittal and transverse mandibular growth is achieved by week 16. The arthritis induction in this study was introduced during a critical period of growth which is analogous with clinical experience of growth disturbances seen in JIA children. Greater significance in inter-group growth differences may be expected if the induction of arthritis had begun earlier than in this study. Masoud *et al.* (1986) also found considerable inter-animal variations during pubertal growth acceleration. This may be a possible reason for the inter-group growth differences at T1 seen in three of the vertical dimensions in groups B, C, and D.

Conclusion

Arthritis in the TMJ reduces mandibular development. The findings of this investigation show that treatment of this condition with IACI may result in even more pronounced mandibular growth reduction than that caused by the arthritis alone. In group A, larger mandibular sagittal and vertical growth was seen compared with the three experimental groups, with the most severe growth reductions seen in group D. Unfavourable posterior rotation of the mandible was observed in all three experimental groups (B, C, and D); however, it was most pronounced in group D.

Caution should be exercised when comparing these findings directly to humans. However, this study does not indicate a promising long-term outcome for the use of repeated IACI in the TMJ as a beneficial early treatment intervention against TMJ involvement in JIA patients. IACI may be indicated for symptomatic relief but should be considered carefully in relation to age and growth maturation.

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