Plasmapheresis, intravenous immunoglobulins and bethametasone – a combined protocol to treat autoimmune congenital heart block: a prospective cohort study

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Abstract

Objective

At the moment there are no standard guidelines for the treatment of autoimmune congenital heart block (CHB). We set out to carry out a prospective cohort study to evaluate the benefits, limits, and safety of a combined therapy protocol to treat antibody-related CHB.

Methods

Twelve consecutive pregnant patients positive to anti-SSA/Ro ± anti-SSB/La antibodies in whom CHB was detected were prospectively evaluated from 2009 to 2014. The treatment protocol consisted of: weekly plasmapheresis, fortnightly intravenous immunoglobulins (IVIG), and daily 4 mg betamethasone from CHB detection until delivery; IVIG was administered to the neonates soon after birth.

Results

At the time CHB was detected, six of the foetuses presented atrioventricular blocks of 2nd degree type and six of 3rd degree type. Two of the foetuses with a 2nd degree block reverted to a 1st degree block and one to a normal atrioventricular conduction. The condition was stable throughout the pregnancy in the other three cases of 2nd degree block. All six 3rd degree blocks were stable during pregnancy and confirmed at birth. After a mean of 37.6 months ± 19.6 SD post-birth, the infants with 1st, normal sinus rhythm, and 2nd degree blocks at birth were all found to be stable. During the follow-up (29 months ± 19.8 SD), pacemakers were implanted in three of the six infants with 3rd degree blocks.

Conclusion

This combined therapy seems to be effective and safe in treating 2nd degree CHB, while its efficacy in treating 3rd degree CHB remains to be established.

Key words

congenital heart block, anti-SSA/Ro antibodies, anti-SSB/La antibodies, plasmapheresis, intravenous immunoglobulins.

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Introduction

Considered the most severe manifestation of neonatal lupus, congenital heart block (CHB) is: an autoantibody mediated disorder presumably caused by placental transmission of maternal autoantibodies to 52-kd and 60-kd SSA/Ro and 48-kd SSB/La ribonucleoproteins which induce inflammation and subsequent fibrosis in the atrioventricular node. The first signs of CHB such as persistent foetal bradyarrhythmias are usually noted between the 18th–24th weeks of gestation (1). Despite frequent reports of foetal cardiac conduction returning to a normal heart rate in both treated and untreated foetuses in whom a 1st degree heart block has been detected (2), CHB appears to be a progressive disease and regression of the 2nd degree type continues to be a debated issue (3, 4). Third-degree or complete heart block seems, instead, to be permanent regardless of treatment (3, 4). While there are no standard guidelines for the management of CHB, treatment generally consists in fluorinated steroids such as dexamethasone or betamethasone. The rationale behind this therapy is founded on the conviction that cardiac injury can be reduced by diminishing the inflammatory component in the foetal conduction system and myocardium. The benefits of fluorinated corticosteroid therapy for CHB detected before birth are, nevertheless, not entirely clear (3, 4). The availability of alternative/additional therapies is for the moment limited to plasmapheresis or intravenous immunoglobulins (IVIG). Plasmapheresis, which significantly lowers the levels of anti-SSA/Ro and anti-SSB/La antibodies in maternal blood (5), reduces their transplacental transfer and could prevent the damage these antibodies can cause the foetal heart. Until now plasmapheresis has mainly been used to prevent CHB occurence, and some studies have described its use also in mothers affected by foetal CHB (6-11). Always performed in conjunction with steroids and administered according to a variety of timetables, the procedure seems to produce no (6, 8, 11) or only partial, transient benefits (7, 9, 10). IVIG is an established therapy for maternal idiopathic thrombocytopenic purpura as well as for neonatal alloimmune thrombocytopenia. Possible mechanisms of action underlying IVIG such as anti-idiotype regulation, inhibition of placental transport of maternal autoantibodies, accelerated clearance of potentially pathogenic autoantibodies, cytokine modulation, complement neutralisation, and modulation of inhibitory signalling in macrophages may explain its role in the treatment of autoimmune CHB (12, 13). Recently utilised as a preventive therapy for anti-SSA/Ro-associated CHB, IVIG seemed to be unable to prevent the recurrence of heart block at the dosage and timing schedules that have been utilised (14, 15). Some attempts have been made to treat women diagnosed with CHB utilising IVIG in conjunction with or without steroids (14, 16, 17). It is important to remember that in those cases the use of IVIG was not, however, systematic throughout the pregnancies, but restricted to a single cycle of therapy. No signs of improvement, but only temporary reversion from a 2nd/3rd degree block to a predominant sinus rhythm, or resolution of echocardiographic signs of myocarditis were noted (14, 16, 17). While the risk of progression to a higher form of heart block continues even during the postnatal period (3, 2, 11, 18), no data has been found concerning IVIG infusions used to treat newborns after birth. IVIG infusions have, instead, been utilised in both mothers during pregnancy and offspring affected with other severe anti-SSA/Ro and/or anti- SSB/La-related cardiac manifestations such as atrial bradycardia or extensive areas of patchy echogenicity to improve those conditions in foetuses and/or in newborns (11, 19).

A combination therapy protocol made up of plasmapheresis, IVIG, and betamethasone throughout pregnancy and IVIG administered to neonates after birth was first described by us in 2011 (20) and other reports have followed (21-23). In view of the rarity of isolated CHB and the difficulty in designing and implementing controlled trials (24) focusing on the treatment of this hazardous disorder, we set out to carry out a prospective cohort study to evaluate the benefits, limits, and safety of this

combined therapy protocol to treat 2nd and 3rd degree antibody-related CHB.

Methods

Study population

Twelve consecutive pregnant patients referred to our attention between January 2009 and September 2014 who were positive to anti-SSA/Ro ± anti-SSB/La antibodies and in whom CHB was detected were prospectively evaluated. The patients' clinical diagnoses were formulated by rheumatologists staffing the outpatient clinic of the Rheumatology Unit of our Institution. Treatment was begun in mothers as soon as possible after CHB was detected by echocardiographic examination performed by the same paediatric cardiologist. IVIG infusions were begun in the neonate within 18 hours of birth. The institutional review board for observational studies and the Audit Committee of the University-Hospital of Padua approved the study design according to the following:

1. the procedures may be considered sufficiently safe both for mother and child;
2. currently, there is no alternative validated treatment for this severe cardiac disease. Thus, once the patients were informed about the disease risks and the potential risks/benefits of the combined therapy, they were asked to sign informed consent forms. Informed consent was obtained from all individual participants included in the study.

Plasmapheresis treatment protocol

Plasmapheresis sessions were performed using a COBE Spectra (Terumo BCT, Lakewood, Co, USA) continuous blood cell flow separator according to the following timetable: daily sessions at onset for the first 2 days and weekly thereafter until the delivery date. As recently demonstrated, once a week plasmapheresis leads to a significant decrease in maternal pathogenic antibody levels (5). The last session was performed the day before the planned delivery. Seventy to 100% of plasma volume was exchanged at each session; the replacement fluid was a mixture of 70% albumin (4%) and 30% saline. Acid Citrate Dextrose Formula A anticoagulant used in a 1:12-1:15 ratio was utilised to ensure anticoagulation. Only subcutaneous arm veins were used as blood access points.

IVIG treatment protocol during pregnancy

IVIG infusions (1g/kg) were scheduled soon after the plasmapheresis sessions at 15 day intervals rather than on two consecutive days once a month, the usual timing used to treat autoimmune disorders. Just as during our previous investigation, the infusions were scheduled using this timetable in the attempt to reduce the amount of infused IVIG removed weekly by the plasmapheresis sessions (25).

The following were considered contraindications to treatment: immunoglobulin A deficiency, renal failure and previous intolerance/allergy to IVIG. Low dose aspirin (100 mg/day), which was suspended a week before the planned delivery, was administered empirically to minimise the IVIG's thrombophilia side effect.

Maternal steroid therapy

Oral betamethasone (4 mg/day) was prescribed to the women at the time they were diagnosed with CHB. After delivery, betamethasone was switched to prednisone (25 mg/day), a therapy which was gradually tapered over the puerperium period unless the mother's clinical condition required continuous steroid treatment.

Monitoring during pregnancy and after birth

All of the patients underwent a physical examination, foetal ultrasound studies, and routine biochemistry testing every two weeks from the time therapy was begun until delivery. Foetal echocardiographies were performed weekly by the same paediatric cardiologist from the time CHB was detected to the end of the pregnancy. The infants underwent echocardiograms and Holter electrocardiograms at birth and every 6 months thereafter unless the heart condition required more frequent monitoring.

IVIG treatment protocol for newborns

Treatment was begun as soon as possible after birth if the infant had at least some serum IgA, normal kidney function, and positivity to maternal antibodies. IVIG infusions (1g/kg) were scheduled at 15 day intervals rather than on two consecutive days every month in the attempt to prevent blood viscosity and excessive plasma volume build-up in the neonates. Slow infusions lasting at least 10 hours during which the infants were opportunely hydrated were carefully monitored. IVIG sessions were continued on this timetable until maternal antibodies were no longer detectable by an enzyme-linked immunosorbent assay (ELISA). When the IgG serum level was higher than that registered at birth, IVIG infusions were instead scheduled once a month. In view of the half-life of IVIG, mothers were advised to begin administering vaccines containing live viruses to children no earlier than at least 3 months after discontinuing IVIG therapy in order to avoid the inactivation of vaccines by the IVIG.

Autoantibody detection

Maternal serum samples were collected at the time CHB was detected and at delivery; newborn serum samples were collected at delivery and before every IVIG infusion. Serum samples were stored at -80°C until 52kd and 60k IgG anti-SSA/Ro and anti-SSB/La antibodies could be assayed using a *home-made* ELISA, following the method described by Klauninger *et al*. with minor modification (26). The cut-off values were calculated as the 99th percentile of results obtained by testing the sera of 100 healthy women. The cut-off for a positive test was 7.7 bound units (BU) for 52 kd anti-SSA/Ro, 6.1 BU for 60 kd anti-SSA/Ro, and 2.0 BU for anti-SSB/La antibodies.

Statistical analysis

The Mann-Whitney U-test was used to compare mean antibody levels at CHB detection with those at delivery and to compare mean maternal antibody levels at delivery with those of the neonates at birth. A p-value <0.05 was considered significant.

Results

Mothers' characteristics

With regard to the patients' assessed

Table I. Clinical and demographic characteristics of the mothers.

Patient number	Age at beginning of pregnancy (years)	Race	Maternal diagnosis	Associated diseases
1	32	Caucasian	SS	Thyroiditis
2	33	Caucasian	UCTD	-
3	32	Caucasian	UCTD	Thyroiditis
4	41	Caucasian	SS	-
5	26	Caucasian	Asymptomatic	-
6	27	Caucasian	Asymptomatic	-
7	25	Caucasian	UCTD	-
8	38	Caucasian	Asymptomatic	-
9	34	Caucasian	Asymptomatic	-
10	36	Caucasian	SS	Thyroiditis
11	38	Caucasian	SS	HCV
12	28	Caucasian	Asymptomatic	Thyroiditis

SS: Sjögren'syndrome; UCTD: undifferentiated connective tissue disease; HCV: hepatitis C virus.

Table II. Pregnancy outcomes.

Patient number	Pregnancy complications	Type of delivery	Weeks at delivery	5 minutes APGAR	Birth weight (% for GE)	Neonatal complications
1	IUGR	Caesarean	35	8	3	-
2	PROM	Caesarean	34	9	50	-
3	IUGR, OH	Caesarean	35	9	5	-
4	OH	Vaginal	36	8	50	-
5	Anhydramnios	Caesarean	33	8	10	-
6	-	Vaginal	36	6	40	RD
7	IUGR, AP	Caesarean	35	8	8	-
8	Anaemia	Caesarean	33	8	15	PA stenosis
9	-	Caesarean	36	9	15	-
10	-	Caesarean	33	8	10	-
11	IUGR	Caesarean	32	8	6	-
12	IUGR	Caesarean	32	7	6	Pneumothorax

GE: gestational age; IUGR: intrauterine growth restriction; PROM: premature rupture of membranes; OH: oligohydramnios; AP: abruptio placentae; RD: respiratory distress; PA: pulmonary artery.

Table III. Heart status of congenital heart block at detection and at birth.

Patient number	At detection			At birth	
	Week	Type of block	Mean bpm	Type of block	Mean bpm
1	20th	2nd	74	1st	158
2	20th	2nd	80	1st	130
3	30th	2nd	74	normal sinus rhythm	140
4	29th	2nd	80	advanced 2nd	80
5	20th	2nd	67	Mobitz ii 2nd	70
6	27th	2nd	70	advanced 2nd	77
7	27th	3rd	63	3rd	85
8	21st	3rd	65	3rd	73
9	24th	3rd	60	3rd	58
10	22nd	3rd	52	3rd	52
11	20th	3rd	45	3rd	44
12	22nd	3rd	56	3rd	58

bpm: beats per minute.

here, cases one and two were first described in the study reported in reference n 20 and cases n. 7, 8, 9 and 10 were first described in reference n. 23. The patients' demographic and clinical characteristics are outlined in Table I. The mothers' mean age at the beginning of the pregnancy was 32.5 years ± 5.2 SD with a range between 25 and 41 years. Four of the women (33.3%) suffered from Sjögren's syndrome, three (25%) from undifferentiated connective tissue disease, five (41.6%) were asymptomatic. Four of the women (33.3%) also suffered from autoimmune thyroiditis and one (8.3%) from hepatitis C infection. Five of the twelve foetal CHB affected mothers were already followed by Rheumatologic Centres before CHB detection. All of them had a mild disease; one (n. 3) at the time of CHB detection was on hydroxychloroquine, while the other patients were untreated. Seven patients were discovered just for CHB detection, five of these were asymptomatic (cases n. 5, 6, 8, 9, 12), one was diagnosed suffering from Sjögren's syndrome (case n. 4) and one from undifferentiated connective tissue disease (case n. 7), both these patients were not treated. The pregnancy outcomes are outlined in Table II. Nine (75%) of the mothers had pregnancy complications and 10 (83.3%) underwent caesarean delivery. Mean gestational age at delivery was 34.2 weeks ± 1.5 SD.

Newborns' characteristics

Five males and seven females (one CHB female was the twin of a healthy male) were born. The mean Apgar score at five minutes was 8±0.8 SD and the mean birth weight in percentiles for gestational age was 18.2±17.7 SD. Three of the infants (25%) presented neonatal complications; one of these underwent successful surgery for pulmonary artery stenosis, while the other two were admitted to intensive care unit due to respiratory distress and pneumothorax, respectively and discharged after a few days.

Features of the atrioventricular block at detection and at birth in each of the infants studied are outlined in Table III. The mean gestational age at the time CHB was detected was 23.5 weeks ± 3.8 SD (range 20–30). There were six 2nd degree blocks (Fig. 1) and six 3rd degree blocks. Three 2nd degree blocks at detection had reverted to a less serious level at birth: two to a first degree block and one to a normal sinus rhythm. One to four weeks after beginning the combined treatment in those foetuses, the 2nd degree block reverted and remained stable until birth and, consequently, mean heart rates showed

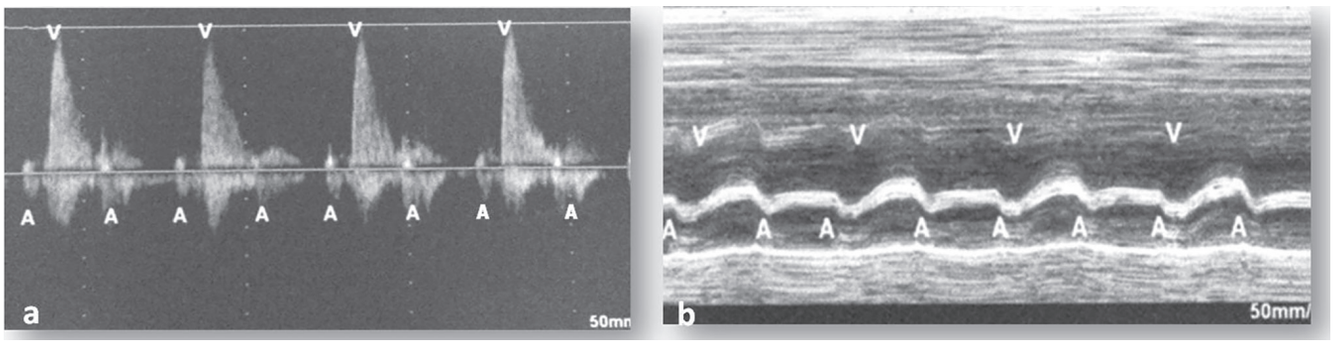

Fig. 1. Doppler (a) and M-mode (b) recordings of the 2nd degree AV blocks of the cases n. 5 and 6, respectively.

marked improvement. The other three cases of 2nd degree blocks at detection have not progressed to the 3rd degree block, but remained unvaried throughout the pregnancies and electrocardiograms at birth identified two advanced and one Mobitz ii 2nd degree blocks (a fixed 2:1 block). All six cases of 3rd degree blocks were stable throughout the pregnancies and were confirmed at birth. In some cases other heart complications were noted at the time CHB was detected. Foetus n. 4 presented rounded hyperechogenic lesions with a 3.5 cm diameter on the posterior wall of the left atrium, which were confirmed at birth but were undetectable 9 months later. Four of the six foetuses with 3rd degree blocks (n. 9, 10, 11 and 12) presented dilated myocardiopathy; which was not confirmed at birth in foetus n. 9 and did not reappear during the 44 month post-natal follow-up period. Intrauterine death, foetal hydrops and other severe cardiac complications were not observed in any of the cases studied. After birth, all the newborns underwent IVIG for a period ranging from 3 to 5 months. Only subcutaneous arm veins were used as blood access points. IVIG infusions were discontinued when passive maternal antibodies were no longer detectable by ELISA assays.

Antibody status in the mothers and newborns

The antibody status in the mothers at the time CHB was detected and at delivery and in the newborns shortly after birth are outlined in Figures 2, 3 and 4. All of the mothers were positive for both anti-52 kd SSA/Ro, anti-60kd SSA/Ro, and 10 (83.3%) were positive also for anti-SSB/La antibodies. Mean anti-52 kd SSA/Ro antibody levels at the time CHB was detected, at the time of delivery, and in the neonates at birth were 992.4 BU ± 1040.1, 197.3±238.9 and 114.0±122.0, respectively (Fig. 2). The difference between mean antibody levels at the time CHB was detected and at delivery was significant (p=0.004). Mean maternal antibody levels at delivery were not significantly different from those of the neonates at birth (p=0.75). Mean anti-60 kd SSA/Ro antibody levels at the time CHB was detected, at delivery, and in the neonates at birth were 1087.2 BU ± 809.2, 228.1±225.0 and 135.0±119.5, respectively (Fig. 3). The difference

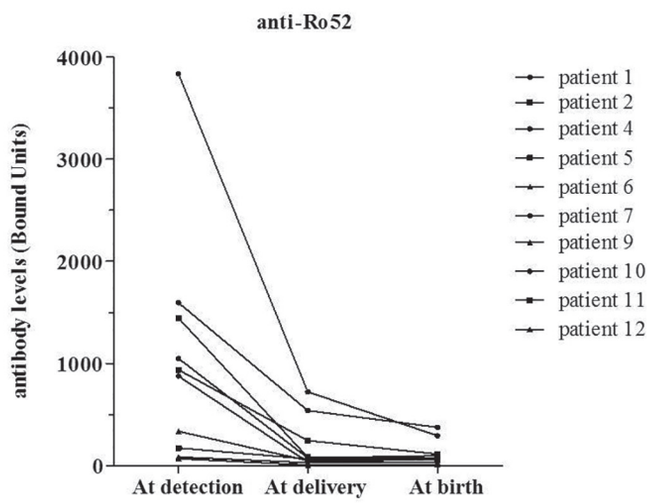

Fig. 2. Levels of anti-52kd SSA/Ro antibodies in the mothers at detection and at the time of delivery and in the infants at birth. Data concerning n 3 and 8 were not available.

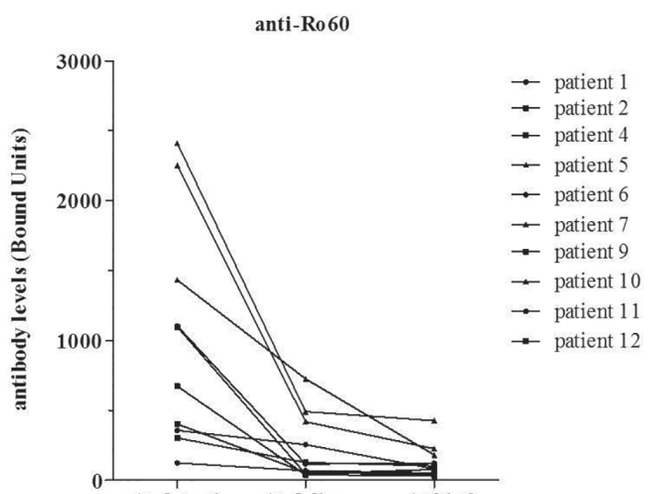

Fig. 3. Levels of anti-60kd SSA/Ro antibodies in the mothers at detection and at the time of delivery and in the infants at birth. Data concerning n 3 and 8 were not available.

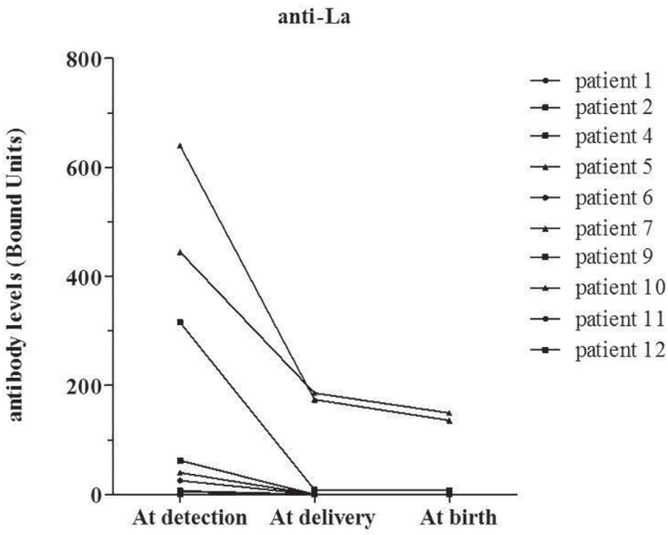

Fig. 4. Levels of anti-SSB/La antibodies in the mothers at detection and at the time of delivery and in the infants at birth. Data concerning n. 3 and 8 were not available.

Table IV. Post-natal follow-up.

Patient number	Follow-up (months)	Type of block	Mean bpm at last Holter ECG	Pacing	Outcome
1	70	1st	97	No	Alive
2	50	1st	92	No	Alive
3	39	normal sinus rhythm	120	No	Alive
4	26	advanced 2nd	58	No	Alive
5	21	Mobitz ii 2nd	54	No	Alive
6	20	advanced 2nd	65	No	Alive
7	45	3rd	72	No	Alive
8	11	3rd	66	No	Alive
9	44	3rd	51	No	Alive
10	51	3rd	48	10 months	Alive
11	17	3rd	37	5 months	Alive
12	6	3rd	40	6 months	Alive

bpm: beats per minute.

between mean antibody levels at the time CHB was detected and at delivery was significant (p=0.002). Mean maternal antibody levels at delivery were not significantly different from those of the neonates at birth (p=0.42). Mean anti-SSB/La antibody levels at CHB detection, at delivery, and in the neonates at birth were 262.1 BU ± 418.5, 205.6±183.7 and 97.9±78.0, respectively (Fig. 4). The difference between mean antibody levels at the time CHB was detected and those at delivery and between mean maternal antibody levels at delivery and those of the neonates at birth were not significantly different (p=0.07 and p=0.5, respectively).

Safety

No remarkable side effects linked to the use of plasmapheresis and IVIG were registered in the mothers, foetuses, or neonates. Whereas maternal complications (Table II) including intrauterine growth restriction (IUGR), premature rupture of membranes (PROM), oligohydramnios and abruptio placentae could be due to the steroid therapy.

Childrens' follow-up

Heart status in the infants after birth is outlined in Table IV. After a mean follow-up of 37.6 months ± 19.6 SD (range 20–70), infants n. 1 and 2 with a 1st degree block, infant n. 3 with a normal sinus rhythm and infants n. 4, 5 and 6 with 2nd degree blocks were found to be stable. The six infants with 3rd degree block at birth continued to be evaluated for a mean of 29 months ± 19.8 SD (range 6–51); during that period permanent pacemakers were implanted in three of the infants (n. 10, 11 and 12) at five, six and ten months, respectively. At the time of writing all the infants are alive and healthy.

Discussion

Due to the difficulty in implementing controlled clinical trials for this rare disorder, no effective therapy strategy has been established for the treatment of 2nd and 3rd degree autoimmune CHB (4, 24). This is the first prospective cohort study aiming to evaluate the efficacy and safety of a combined therapy protocol based on weekly plasmapheresis, fortnightly IVIG, and daily betamethasone used to treat foetal CHB related to maternal anti-SSA/Ro and anti-SSB/La antibodies. Three of the six foetuses affected with 2nd degree block reverted two to a 1st degree block and one to a normal atrioventricular conduction, respectively, during the pregnancy itself; a 1st degree block was found in the two cases and a normal sinus rhythm in the third at birth and during the post-birth follow-up. The other three cases of 2nd degree block did not progress to a 3rd degree block, but were stable at birth and throughout the postnatal follow-up. The six cases of 3rd degree block were likewise unvaried; three of these required pacemaker implantation. There were no complications such as intrauterine foetal death, hydrops or neonatal death, which are frequently described in foetuses with complete CHB (27), in any of the six cases studied.

On the basis of these results, we could deduce that, an improvement in atrioventricular block is possible only in the early stages of injury when inflammation in the atrioventricular node and surrounding myocardium is still reversible and before the tissues have become fibrotic and calcific (28). This hypothesis would explain the reversion or the non-progression to 3rd degree block noted in the six consecutively followed foetuses with a 2nd degree block and the substantial unresponsiveness of those with 3rd degree blocks. The efficacy of the combined therapy is thus strictly tied to the early detection of an incomplete CHB and rapid treatment onset. On the basis of these observations, pregnant women positive to anti-SSA/Ro and anti-SSB/La

antibodies should routinely undergo at least weekly monitoring of foetal heart rate between the 18th and 26th weeks of gestation. It has, in fact, been demonstrated that a complete block and cardiomyopathy can occur within one week of a normal echocardiogram (29).

The rationale behind the therapeutic strategy outlined here was based on the benefits that could be gained by summing the effects of the three therapies: betamethasone could reduce inflammation of the foetal conduction system and myocardium, plasmapheresis could, as has been demonstrated (5) and confirmed in this study, remove a large quantity of the offending autoantibodies from the maternal-foetal circulation, and IVIG could counteract the effect of the remaining autoantibodies. It can also be hypothesised that IVIG therapy can additionally treat foetal cardiac injury thanks to its transplacental passage. Used singularly, steroids (4), plasmapheresis (9, 10) and IVIG (14, 16, 17) seem to be unable to prevent progression of 2nd degree to 3rd degree CHB. The idea of treating CHB using a combination therapy was based on previous experiences in managing high risk pregnancies in patients with antiphospholipid syndrome in whom a combined protocol including weekly plasmapheresis and fortnightly IVIG infusions along with anti-thrombotic treatment was found to be effective and safe (25, 30). A similar type of treatment is also recommended in the event of catastrophic antiphospholipid syndrome, another autoantibody-related devastating disease (31). It is interesting that a combined PE/IVIG therapy already since 2000 has been observed to be beneficial and safe in other immunological disorders such as when patients positive for panel-reactive antibodies are desensitised before organ transplantation (32), or during the control of humoral allograft rejection (33) or maternal-foetal incompatibilities (34).

While damage to the heart conduction system usually occurs during pregnancy, there is still risk of progression to a more serious heart block even after birth (4, 9, 16, 18). As demonstrated by the finding in our patients that mean anti-52 kd SSA/Ro, anti-60 kd SSA/Ro and anti-SSB/La antibody levels in infants soon after birth were not significantly different from those of the mothers at delivery, postnatal heart damage is probably due to the presence of passive maternal pathogenic antibodies in the blood of neonates. The idea of subjecting newborns to IVIG treatment soon after birth was based on our own experience while monitoring case n.1, which is outlined in this study and described extensively elsewhere (20). In that case, after a short period during which the foetus presented a 1st degree block, 19 hours after birth he progressed to a 2nd degree Wenckebach type block; at that point we decided to prescribe IVIG which provoked a prompt and permanent regression to the initial 1st degree block.

The safety of both plasmapheresis and IVIG procedures during pregnancy has been verified by other studies (25, 35, 36). Also employed to treat other neonatal diseases such as alloimmune thrombocytopenia, IVIG therapy may be considered a demanding but safe procedure for newborns (37). No remarkable side effects were observed in mothers or infants during plasmapheresis or IVIG treatments. Possibly linked to prolonged steroid therapy, some pregnancy complications including IUGR, PROM and decrease in amniotic fluid causing a low gestational age at delivery and a low birth weight were noted. On the basis of these results and recent literature data (38) attributing to steroids no efficacy for CHB treatment, the dosage of steroid has been changed currently, so, betametasone 4 mg/day is administered only the first month after CHB detection, then it is gradually tapered during the remaining pregnancy time in order to reduce steroid side effects.

The limits characterising this study include the small number of cases included in the study sample and the high cost of treatment. Given the rarity of the disorder and its severity, the possibility of successfully treating mothers/foetuses could justify the expense and energy involved. The encouraging results of our small prospective study cannot support routine use of the combined therapy, but they could serve as the starting point for a multicentre study designed to evaluate the benefits and limits of this particular therapy in 2nd degree CHB in a larger cohort of patients. Its efficacy in treating 3rd degree CHB remains to be established and currently this treatment cannot be recommended in such condition.

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References

1. BUYON JP, HIEBERT R, COPEL J *et al*.: Autoimmune associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 1998; 31: 1658-66.
2. SONESSON SE, SALOMONSSON S, JACOBSSON LA, BREMME K, WAHREN-HERLENIUS M: Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. *Arthritis Rheum* 2004; 50: 1253-61.
3. ELIASSON H, SONESSON SE, SHARLAND G *et al*.: Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation* 2011; 124: 1919-26.
4. FRIEDMAN DM, KIM MY, COPEL JA, LLANOS C, DAVIS C, BUYON JP: Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study. *Am J Cardiol* 2009; 103: 1102-6.
5. TONELLO M, RUFFATTI A, MARSON P *et al*.: Plasma exchange effectively removes 52- and 60-kDa anti-Ro/SSA and anti-La/SSB antibodies in pregnant women with congenital heart block. *Transfusion* 2015; 55: 1782-6.
6. ARROYAVE CM, PUENTE LEDEZMA F, MONTIEL AMOROSO G, MARTÍNEZ GARCÍA AC: Myocardiopathy diagnosed in utero in a mother with SS-A antibodies treated with plasmapheresis. *Ginecol Obstet Mex* 1995; 63: 134-7.
7. BUYON JP, SWERSKY SH, FOX HE, BIERMAN FZ, WINCHESTER RJ: Intrauterine therapy for presumptive fetal myocarditis with acquired heart block due to systemic lupus erythematosus. Experience in a mother with a predominance of SS-B (La) antibodies. *Arthritis Rheum* 1987; 30: 44-9.
8. HERREMAN G, GALEZOSKI N: Maternal connective tissue disease and congenital heart block [letter]. *N Engl J Med* 1985; 1312-29.
9. RUFFATTI A, FAVARO M, COZZI F *et al*.: Anti-SSA/Ro-related congenital heart block in two family members of different generations: comment on the article by Clancy *et al*. *Arthritis Rheum* 2005; 52: 1623-25.
10. SALEEB S, COPEL J, FRIEDMAN D, BUYON JP: Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research

registry for neonatal lupus. *Arthritis Rheum* 1999; 42: 2335-45.
11. ZEMLIN M, BAUER K, DÖRNER T, ALTINÖZ H, VERSMOLD H: Intrauterine therapy and outcome in four pregnancies of one mother with anti ro-autoantibody positive Sjogren's syndrome. *Z Geburtshilfe Neonatol* 2002; 206: 22-5.
12. ROUTSIAS JG, KYRIAKIDIS NC, FRIEDMAN DM *et al*.: Association of the idiotype: anti-idiotype antibody ratio with the efficacy of intravenous immunoglobulin treatment for the prevention of recurrent autoimmune-associated congenital heart block. *Arthritis Rheum* 2011; 63: 2783-9.
13. YU Z, LENNON VA: Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *N Engl J Med* 1999; 340: 227-8.
14. FRIEDMAN DM, LLANOS C, IZMIRLY PM *et al*.: Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: results of a multicenter, prospective, open-label clinical trial. *Arthritis Rheum* 2010; 62:11-46.
15. PISONI CN, BRUCATO A, RUFFATTI A *et al*.: Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. *Arthritis Rheum* 2010; 62: 1147-52.
16. BRUCATO A, RAMONI V, GEROSA M, PISONI MP: Congenital fetal heart block: a potential therapeutic role for intravenous immunoglobulin. Author reply. *Obstet Gynecol* 2011; 117: 77.
17. DAVID AL, ATAULLAH I, YATES R, SULLIVAN I, CHARLES P, WILLIAMS D: Congenital fetal heart block: a potential therapeutic role for intravenous immunoglobulin. *Obstet Gynecol* 2010; 116 (Suppl. 2): 543-7.
18. ASKANASE AD, FRIEDMAN DM, COPEL J *et al*.: Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. *Lupus* 2002; 11: 145-51.
19. TRUCCO SM, JAEGGI E, CUNEO B *et al*.: Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. *J Am Coll Cardiol* 2011; 57: 715-23.
20. RUFFATTI A, MILANESI O, CHIANDETTI L *et al*.: A combination therapy to treat second-degree anti-Ro/La-related congenital heart block: a strategy to avoid stable third-degree heart block? *Lupus* 2012; 21: 666-71.
21. DI MAURO A, CAROLI CASAVOLA V, FAVIA GUARNIERI G, CALDERONI G, CICINELLI E, LAFORGIA N: Antenatal and postnatal combined therapy for autoantibody-related congenital atrioventricular block. *BMC Pregnancy Childbirth* 2013; 13: 220.
22. MARTÍNEZ-SÁNCHEZ N, ROBLES-MARHUENDA Á, ÁLVAREZ-DOFORNO R *et al*.: The effect of a triple therapy on maternal anti-Ro/SS-A levels associated to fetal cardiac manifestations. *Autoimmun Rev* 2015; 14: 423-8.
23. RUFFATTI A, MARSON P, SVALUTO-MOREOLO G *et al*.: A combination therapy protocol of plasmapheresis, intravenous immunoglobulins and betamethasone to treat anti-Ro/La-related congenital atrioventricular block. A case series and review of the literature. *Autoimmun Rev* 2013; 12: 768-73.
24. COSTEDOAT-CHALUMEAU N, IZMIRLY P, CLANCY R *et al*.: Letter to the Editor in response to the article "Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials." by Gleicher N, Elkayam UP *Autoimmun Rev* 2013;12:1039-1045. *Autoimmun Rev* 2014; 13: 70-2.
25. RUFFATTI A, MARSON P, PENGO V *et al*.: Plasma exchange in the management of high risk pregnant patients with primary antiphospholipid syndrome. A report of 9 cases and a review of the literature. *Autoimmun Rev* 2007; 6: 196-202.
26. KLAUNINGER R, SKOG A, HORVATH L *et al*.: Serological follow-up of children born to mothers with Ro/SSA autoantibodies. *Lupus* 2009; 18: 792-8.
27. BRUCATO A, GRAVA C, BORTOLATI M *et al*.: Congenital heart block not associated with anti-Ro/La antibodies: comparison with anti-Ro/La-positive cases. *J Rheumatol* 2009; 36: 1744-8.
28. ANGELINI A, MOREOLO GS, RUFFATTI A, MILANESI O, THIENE G: Images in cardiovascular medicine: calcification of the atrioventricular node in a fetus affected by congenital complete heart block. *Circulation* 2002; 105: 1254-5.
29. FRIEDMAN DM, KIM MY, COPEL JA *et al*.: Utility of cardiac monitoring in fetuses at risk for congenital heart block. The PR interval and dexametasone evaluation (PRIDE) prospective study. *Circulation* 2008; 117: 485-93.
30. RUFFATTI A, SALVAN E, DEL ROSS T *et al*.: Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positività. A European multicentre retrospective study. *Thromb Haemost* 2014; 112: 727-35.
31. CERVERA R, RODRÍGUEZ-PINTÓ I, ESPINOSA G ON BEHALF OF THE TASK FORCE ON CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME: Catastrophic antiphospholipid syndrome: Task Force report summary. *Lupus* 2014; 23: 1283-5.
32. MONTGOMERY RA, ZACHARY AA, RACUSEN LC *et al*.: Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation* 2000; 70: 887-95.
33. IBERNON M, GIL-VERNET S, CARRERA M *et al*.: Therapy with plasmapheresis and intravenous immunoglobulin for acute humoral rejection in kidney transplantation. *Transplant Proc* 2005; 37: 3743-5.
34. FERNANDEZ-JIMENEZ MC, JIMENEZ-MARCO MT, HERNANDEZ D, GONZALEZ A, OMENACA F, DE LA CAMARA C: Treatment with plasmapheresis and intravenous immunoglobulin in pregnancies complicated with anti-PP1Pk or anti-K immunization: a report of two patients. *Vox Sang* 2001; 80: 117-20.
35. BOSCH T: Therapeutic apheresis—state of the art in the year 2005. *Ther Apher Dial* 2005; 9: 459-68.
36. EL-HAIEG DO, ZANATI MF, EL-FOUAL FM: Plasmapheresis and pregnancy outcome in patients with antiphospholipid syndrome. *Int J Gynaecol Obstet* 2007; 99: 236-41.
37. BRANCH DW, PORTER TF, PAIDAS MJ *et al*.: Obstetric uses of intravenous immunoglobulin: successes, failures and promises. *J Allergy Clin Immunol*, 2001; 108: S133-8.
38. LEVESQUE K, MOREL N, MALTRE A *et al*.: Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. *Autoimmun Rev* 2015; 14: 1154-60.