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Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis

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ABSTRACT

Aim: To investigate the therapeutic value of azathioprine as monotherapy or combined with other immunosuppressive drugs for uveitis in patients with juvenile idiopathic arthritis (JIA).

Methods: Retrospective multi-center study including 41 JIA children (28 (68.2%) female) with unilateral or bilateral (n=28) chronic anterior uveitis. Azathioprine was used to treat uveitis that was active in patients on topical or systemic corticosteroids, MTX, or other immunosuppressive drugs. The primary endpoint was assessment of uveitis inactivity. Secondary endpoints comprised dose sparing of topical steroids and systemic corticosteroids and immunosuppression.

Results: At 1 year, uveitis inactivity was achieved in 13/17 (76.5%) of patients by using azathioprine as systemic monotherapy and in 5/9 (56.6%) as combination therapy. During the entire azathioprine treatment period (mean 26 months), inactivity was obtained in 16/26 patients (61.5%) with monotherapy and in 10/15 (66.7%) when combined with other immunosuppressives (p=1.0). With azathioprine, dosages of systemic immunosuppression and steroids could be reduced by ≥50% (n=12) or topical steroids reduced to ≤2 drops/eye/day in 6 patients. In 3 patients (7.3%), azathioprine was discontinued because of nausea and stomach pain.

Conclusions: "Azathioprine may be reconsidered in the step-ladder approach for the treatment of JIA-associated uveitis. The addition of azathioprine may also be beneficial for patients not responding properly to methotrexate."

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in childhood and begins before 16 years of age. JIA is characterized by a chronic inflammation of the joints, which may lead to joint destruction.[1-3] The most frequent form of eye involvement in JIA is uveitis, with an estimated incidence between 10 and 18%.[4-5] Uveitis is characterized by chronic inflammation of the iris and ciliary body. The course of the disease varies highly. A severe and vision-threatening course develops in approximately one third of patients, and the complication rate rises during the chronic course of disease.[5-7]

The aim of treatment is to completely abolish active inflammation in the eye. Therapy is usually started with topical corticosteroids, occasionally combined with systemic corticosteroids. However, in approximately 30% of patients the uveitis remains active, so that immunosuppressive drugs are required. Methotrexate is the first-choice immunosuppressive, cyclosporine A, azathioprine or the anti-tumor necrosis factor (TNF) alpha inhibitors represent other options.

Azathioprine is a well-known purine synthesis inhibitor that is widely used in organ transplantation and several autoimmune diseases, e.g., rheumatoid arthritis. A favorable response has also previously been noted in the treatment of arthritis in JIA patients.[8-9]

Azathioprine has only occasionally been utilized to treat uveitis in JIA patients. Indeed, only small case series have been reported in the literature, describing experience with azathioprine in only few children. [9-10] In this

paper, we summarize our observations using azathioprine in treating 41 patients with JIA-associated uveitis.

Patients and Methods

All patients in this study fulfilled the classification of juvenile idiopathic arthritis (JIA) in agreement with the International League of Associations for Rheumatology (ILAR) criteria.[3] The 41 children were treated with azathioprine for severe chronic anterior uveitis. The cohort included consecutive patients who were started on azathioprine treatment for uveitis between 1995 and 2007. Charts were reviewed retrospectively. The design of the work conforms to the standards currently applied in Germany. No institutional review board approval is required for chart review studies.

Rheumatologic examinations and diagnostic procedures included a review of systems, laboratory tests (e.g., antinuclear antibodies, rheumatoid factor, and HLA B 27), urine analysis, and chest x-ray, if necessary. An infectious etiology was excluded if serological tests for EBV, CMV, HSV, HZV, treponema, toxoplasma, and toxocara and the tuberculosis skin test were negative.

Patients with other uveitis entities, such as intermediate, Fuchs heterochromic cyclitis, and infectious uveitis syndromes, were excluded from the study. A standardized ophthalmic database was applied for the analysis. The ophthalmic assessment included best-corrected visual acuities (BCVA), slit-lamp examination, tonometry (Goldmann), and funduscopy.

Uveitis was defined and anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group recommendations.[11] The presence of ≥ 1+ cells in the anterior chamber was defined as active uveitis. We documented the duration of uveitis and whether disease was uni- or bilateral. Dates of first and final azathioprine treatments were noted, as were azathioprine dosage, adverse effects, any topical and anti-inflammatory medication before and during azathioprine treatment, and initial manifestation of uveitis in the fellow eye after beginning azathioprine treatment. Additionally, the uveitis-related complications in the eye were analyzed, as central band-keratopathy, new synechiae formation, cataract, vitreous opacity, phthisis and glaucoma. Data were collected from all patients at 6- to 12-month intervals.

Azathioprine monotherapy was instituted in patients with active uveitis, if they were being treated with topical (≥3 drops/day) and possibly also systemic corticosteroids (≥ 10mg, or ≥ 0.15 mg/kg body weight), or in order to spare systemic corticosteroids. Moreover, azathioprine was considered as an additional immunosuppressive if uveitis remained active under treatment with any other immunosuppressive drug.

The dosages of systemic corticosteroids and immunosuppressive drugs were altered or medication discontinued according to the clinical assessment of arthritis and uveitis activity and to the medication-related side effects.

After 1 year of azathioprine treatment and at all visits during the entire treatment period, the response to treatment, as defined by inactivity of uveitis, and nonresponse, as defined by activity of uveitis, were analyzed. Inactivity of anterior uveitis was defined as < 1+ cells in the anterior chamber.[11]

Response to treatment with azathioprine was additionally judged according to a modified grading system described by Saurenmann et al..[12] Briefly, good response was defined as a decrease ≥ 50% in both corticosteroid use and immunosuppressives (if not on combined immunosuppressive drug and systemic corticosteroid at institution of azathiopine, then only reduction of corticosteroids ≥ 50%); moderate response, reduction ≥50% in either corticosteroid or immunosuppressive drug; and poor response, reduction of <50% in both corticosteroid and immunosuppressive drug. In this study, dose sparing was assessed independently for systemic and topical steroids.

All analyses were performed using MedCalc software (MedCalc Version 9.6.4.0, MedCalc Software, Mariakerke, Belgium). The t test, chi-square test and Fisher´s exact test for categorical data were applied for statistical analysis when appropriate. A p-value < 0.05 was considered as a significant difference.

Results

A total of 41 children were included in this study. All children had JIA and associated active chronic anterior uveitis. Demographic characteristics including JIA subgroups and uveitis are listed in Table 1. Notably, the majority of patients suffered from early-onset arthritis and showed a severe course of uveitis, with complications already present at the initial visit in nearly half of the patients, e.g. central band-keratopathy (n=5), cataract (n=20), vitreous opacity (n=5), and glaucoma (n=12). All of the patients had previously received topical corticosteroids, and 29.3% had immunosuppressive drugs. The follow-up after instituting azathioprine was 26 months (mean, range 3-107). Azathioprine was started at a mean dosage of 2.4

mg/kg body weight (range 1.4 to 3.2). Then, azathioprine was continued, and the mean dosage at the end of the study period was 2.1 mg/kg body weight daily (range 1.0 to 2.8) (p=0.047).

Effect of azathioprine monotherapy on uveitis

Of the 26 patients who initially received azathioprine monotherapy (fig 1) for uveitis, inactivity of uveitis was achieved in 16 (61.5%), while inflammation recurred or persisted in the other 10 (38.5%). Mean follow-up was 26 months (Table 2). Response to treatment did not correlate well with JIA subgroup (p=1.0), age at onset of arthritis (p=0.76), ANA positivity (p=1.0), gender (p=0.12), age at onset of uveitis (p=0.41), bilateral uveitis (p=1.0), and presence of complications at initial presentation (p=1.0).

A significant interpatient variation was observed in the dose-sparing effect of immunosuppressive drugs and topical steroids. New uveitis complications were noted in 3 of 26 patients in at least one eye during the treatment period (Table 2).

Effect of azathioprine in combination with other disease-modifying antirheumatic drugs on uveitis

Of the 41 patients included, azathioprine was given in combination with other immunosuppressive drugs in 15 patients (Table 3, fig 1). While azathioprine was added to previous immunosuppression in 13 patients, other immunosuppressive drugs were then added to the regimen in another 2 patients with active uveitis under azathioprine. Whereas in 7 patients,

azathioprine was combined with methotrexate, azathioprine was combined with cyclosporine A in 5 patients and with other immunosuppressive drugs (Leflunomid, Adalimumab, Etanercept) in another 3 patients. In 10 of 15 patients (66.7%) treated with azathioprine in combination with other immunosuppressive drugs inactivity of uveitis was achieved. It is worthy of note that the response to azathioprine treatment analyzed at 1 year and for the entire period (mean 24 months) did not differ from the group of patients treated for uveitis with azathioprine monotherapy (p=1.0)

The outcome of azathioprine in combination with other immunosuppressive drugs with regard to sparing the dose of the other systemic immunosuppressive agents or corticosteroids was good in 6, moderate in 4, and poor in 5 patients (Table 3). In this respect, the difference between the azathioprine mono- and combination therapy failed to reach the level of significance (p=0.23). In this group, topical steroids could be tapered off in 6 patients, while the dosage was unchanged in another 9. The sparing effect of topical steroids was not better than in the monotherapy group (p=0.42).

The observations with azathioprine given in combination with methotrexate or cyclosporine A, which are commonly used to treat uveitis associated with JIA, are summarized in Table 4 and 5. Although the numbers of patients in both of the groups are fairly small, the observations suggest that uveitis inactivity may be achieved with the combined use of methotrexate or cyclosporine A with azathioprine. However, the sparing effect of topical and systemic corticosteroids and immunosuppressive drugs was moderate to poor in the majority of cases.

New complications and side effects under azathioprine

Twenty patients (49%) had already developed uveitis complications before azathioprine therapy was instituted. However, the first or additional uveitis complications were noted in another 7 patients while under azathioprine treatment.

During the treatment period with azathioprine monotherapy, 3 of the 26 patients (11.5%) developed new secondary complications. Four of the 15 patients under systemic combination therapy (26.7%) were reported to have developed new uveitis complications, and these numbers did not differ from the azathioprine monotherapy group (p=0.41).

Azathioprine was withdrawn in 3 patients because of nausea. Apart from this, no other serious side effects were documented during the study period.

Discussion

Only very few small case series have assessed the value of azathioprine to treat uveitis in patients with associated JIA.[8,9] The observations from our multi-center study show that this agent may be helpful as systemic monotherapy or in combination with other immunosuppressive agents. Azathioprine may also be useful for long-term therapy and shows a dose-sparing effect for corticosteroids or immunosuppression.

The pathogenesis of uveitis in JIA patients is not well defined. The few published histopathological papers demonstrated that the disease is marked by nongranulomatous inflammation in the iris and ciliary body. [13-15] A recently published paper showed that the cellular infiltration mostly consisted

of plasma cells, plasmocytic lymphocytes and monocytes, and few T cells. In light of these findings, the poor response to cyclosporine A that was described most recently is not surprising, suggesting that JIA uveitis may not be primarily a T cell-mediated disease.[16] The focal aggregates mainly consisted of CD20 positive B cells: primarily IgG B cells and only few IgM B cells.[17] However, as the infiltrate at nucleation may not reflect that during early active disease, the therapeutic implications of end-stage histology are limited.

Azathioprine is a purine nucleoside analog. It interferes with adenine and guanine ribonucleotides by suppressing inosinic acid synthesis, which in turn interferes with DNA replication and RNA transcription. [18] Immunologically, azathioprine decreases the numbers of peripheral T and B lymphocytes and reduces mixed lymphocyte reactivity, interleukin-2 synthesis, and IgM production.[19-20] In addition, the production of cytokines such as IFN-y and TNF in T lymphocytes is inhibited and apoptosis of these cells is initiated.[21]

Azathioprine is well absorbed orally and cleaves to 6-mercaptopurine, which is metabolized to thioinosinic and thioguanylic acid by the hypoxanthine phosphoribosyltransferase. These metabolites affect ribonucleotide synthesis.[22] Therefore, azathioprine appears to be an appropriate candidate drug for uveitis in JIA. Azathioprine has also been introduced for the treatment of uveitis associated with JIA.[8,9]

Savolainen et al.[9] reported that in the long term azathioprine could effectively treat arthritis in 129 patients with JIA. In this study, a total of 19 patients had chronic iridocyclitis in some phase of the disease. Three children

had episodes before treatment with azathioprine and 14 patients had active uveitis when included in study. In the latter cases activity persisted during therapy. Iridocyclitis occurred for the first time in 2 patients during low-dose therapy. In contrast to our study, no specific time points were analyzed, the cell grade in the anterior chamber as a measure for activity was not specified as currently agreed, nor was the adjustment of the topical steroid treatment considered.[11] It may be speculated that additional topical treatment was not adjusted properly to the inflammatory activity.

Hemady et al. examined the role of immunosuppressive drugs in the management of progressive, corticosteroid-resistant uveitis associated with JIA.[10] The mean duration of immunosuppressive therapy was 6.4 months. Only four of 26 patients were treated with azathioprine. In 2 patients inflammation was controlled. The other two patients –one receiving azathioprine in combination with methotrexate- did not respond to the therapy.

In contrast to the rare published data, our observations in a larger and homogenous group of JIA patients suggest that azathioprine may be effective in the treatment of JIA-associated chronic anterior uveitis (). During the mean follow-up of 26 months under azathioprine monotherapy, uveitis inactivity was maintained in 16 of 26 children (61.5%). The sparing effect of anti-inflammatory medication, however, differed markedly among the individuals.The effectiveness of other immunosuppressive drugs in the treatment of JIA-associated uveitis has also been investigated only in retrospective uncontrolled studies. In one study including 23 patients, remission was described in 417 of 661 months with MTX treatment [23]. In

another study, quiescence of uveitis was obtained with MTX in 32 of 35 patients [24]. Inactivity of uveitis was noted with cyclosporine A in only 6 of 25 patients [16].

The impact of azathioprine on the visual outcome could not be determined in this study, as the documented visual acuities were frequently unreliable due to children's incompliance or because of opacities in the visual axis. Although this case series did not include a control group, the data reveal that new uveitis complications occurred in some patients during the treatment period. Indeed, new complications were detected in 3 of the 26 patients (11.5%) included, and in 2 of the patients the first uveitis manifestation developed in the formerly uninvolved eye although they were being treated with azathioprine.

Currently, the first-choice immunosuppressive drug is MTX, which is quite effective in controlling uveitis in JIA patients.[23,24] The management of JIA children with uveitis who do not respond to MTX represents an important issue, as this is the most frequently used immunosuppressant in these patients. It is, therefore, noteworthy that our data show that azathioprine was not less effective when it was added to an immunosuppressive drug already being given. When azathioprine was added to MTX in the children with active uveitis in our case series, inactivity was achieved in 71.4%. However, our observations show that the sparing effect of the other systemic immunosuppressive drugs and of topical steroids can vary. For the entire patient series, systemic immunosuppressive drugs and steroids could be reduced only in a minority of patients. It is possible that the similar outcomes with azathioprine monotherapy and combination therapy are due to the differences in severity between the groups. However, uveitis activity, duration

of uveitis, and complication rates did not differ between the groups (data not shown)."

Although we could speculate that higher azathioprine dosages would have given better results in this study, the azathioprine dosages did not differ significantly between the responders and the nonresponders (monotherapy p=0.3 and combined therapy p=1.0). According to safety recommendations, the dosage for this patient group should be under 3 mg/kg body weight. It has been shown previously that azathioprine treatment at this dosage is safe and well-tolerated in children.[25]

Apart from the anti-inflammatory value of immunosuppressive agents, drug safety is of the outmost importance in JIA children with uveitis, especially as long-term treatment is usually required. Thus, long-term safety data are needed, which is a good reason for preferentially using particular drugs, e.g., MTX, Cyclosporine A and also azathioprine. Therefore, the use of azathioprine may be favored in patients who do not respond to MTX, and may be an alternative to some recently introduced drugs, e.g., TNF-alpha inhibitors, leflunomide, or mycofenolate mofetil.

In summary, the present data suggest that azathioprine may be reconsidered in the step-ladder approach for the treatment of children with JIA-associated uveitis. Although this study is somewhat limited by its retrospective design and short follow-up in some patients, the results suggest that the value of azathioprine monotherapy is higher than often believed. The addition of azathioprine may also be beneficial for patients not responding properly to other immunosuppressive drugs. Prospective randomized studies and long-

term registries are necessary to define the most effective and safest treatment regimen.

Figure 1

Azathioprine for uveitis in 41 children with juvenile idiopathic arthritis.

Table 1

Patient chracteristics before treatment with azathioprine. Children with uveitis associated with juvenile idiopathic arthritis (JIA). JIA subgroups are classified according to the ILAR classification (n=41). Antinuclear antibodies (ANA), Aza = azathioprine.

Juvenile idiopathic arthritis	41 (100%)
Oligoarthritis	35 (85.4%)
Polyarthritis	2 (4.9%)
Enthesitis related arthritis	1 (2.4%)
Other arthritis	3 (7.3%)
ANA positivity	39 (95.1%)
Active chronic anterior uveitis	41 (100%)
Uni-/bilateral	13 (31.7%) / 28 (68.3%)
Any uveitis complication	20 (48.8%)
Female / male	28 (68.3%) / 13 (31.7%)
Mean age at onset of arthritis (yrs)	3.6 (range 1 – 15)
Mean age at onset of uveitis (yrs)	4.38 (range 1 – 15)
Mean duration of uveitis before study (yrs)	2,82 (range 0-19)
Previous topical corticosteroid treatment	41 (100%)
Previous systemic DMARDs	
No others	29 (70.7%)
Methotrexate	10 (24.4%)
Cyclosporine A	6 (14.6%)
Etanercept	1 (2.4%)
Prednisolone	0 (0%)
Mean follow-up time on Aza (months)	25 (range 3-107)

DMARDs = disease-modifying antirheumatic drugs

Table 2

Azathioprine monotherapy as initial immunosuppressive treatment. (n=26). Uveitis in patients with juvenile idiopathic arthritis (JIA). Inactivity of anterior uveitis was defined as < 1+ cells in the anterior chamber.[11] *Sparing of second-line immunosuppressive drugs and topical steroids according to Saurenmann et al..[12]. During entire follow-up = at all study visits.

	At 1 year n (%)	During entire follow-up (mean 2.2 years)
Inactivity of uveitis	13 / 17 (76.5%)	16 / 26 (61.5%)
New uveitis complications	nd	3 (11.5%)
Sparing of systemic immunosuppression*		
Good	nd	6 (23.0%)
Moderate	nd	13 (50.0%)
Poor	nd	7 (27.0%)
Sparing of topical steroids		
Taper off	9 (53.0%)	7 (27.0%)
Reduce to ≤ 2 drops / d	4 (23.5%)	6 (23.0%)
Unchanged	3 (17.6%)	8 (30.8%)
Increased	1 (5.9%)	5 (19.2%)

Table 3

Azathioprine when added to treatment of patients already on any immunosuppressive drugs (n=15). Uveitis in patients with juvenile idiopathic arthritis (JIA). Inactivity of anterior uveitis was defined as < 1+ cells in the anterior chamber.[11] *Sparing of second-line immunosuppression and topical steroids according to Saurenmann et al..[12] During entire follow-up = at all study visits.

	At 1 year n (%)	During entire follow-up (mean 2.2 years)
Inactivity of uveitis	5 / 9 (56.6%)	10 / 15 (66.7%)
New uveitis complications	2 (22.2%)	3 (20.0%)
Sparing of systemic immunosuppression*		
Good	nd	6 (40.0%)
Moderate	nd	4 (26.7%)
Poor	nd	5 (33.3%)
Sparing of topical steroids		
Taper off	1 (11.1%)	6 (40.0%)
Reduce to ≤ 2 drops / d	2 (22.2%)	0 (0%)
Unchanged	3 (33.3%)	9 (60.0%)
Increased	3 (33.3%)	0 (0%)

Table 4

Azathioprine when added to treatment of patients already on methotrexate (n=7). Uveitis in patients with juvenile idiopathic arthritis (JIA). Inactivity of anterior uveitis was defined as < 1+ cells in the anterior chamber.[11] *Sparing of second-line immunosuppression and topical steroids according to Saurenmann et al..[12]. During entire follow-up = at all study visits.

	At 1 year n (%)	During entire follow-up (mean 1.4 years)
Inactivity of uveitis	4 / 7 (57.1%)	5 / 7 (71.4%)
New uveitis complications	2 (28.6%)	3 (42.6%)
Sparing of systemic immunosuppression*		
Good	nd	2 (28.6%)
Moderate	nd	2 (28.6%)
Poor	nd	3 (42.9%)
Sparing of topical steroids		
Taper off	1 (14.3%)	1 (14.3%)
Reduce to ≤ 2 drops / d	2 (28.6%)	0 (0%)
Unchanged	3 (42.9%)	5 (71.4%)
Increased	1 (14.3%)	1 (14.3%)

Table 5

Azathioprine when added to treatment of patients already on cyclosporine A (n=5). Uveitis in patients with juvenile idiopathic arthritis (JIA). Inactivity of anterior uveitis was defined as < 1+ cells in the anterior chamber.[11] *Sparing of second-line immunosuppression and topical steroids according to Saurenmann et al..[12] During entire follow-up = at all study visits.

	At 1 year n (%)	During entire follow-up (mean 2.2 years)
Inactivity of uveitis	2 / 4 (50.0%)	3 / 5 (60.0%)
New uveitis complications	0 (0%)	2 (40.0%)
Sparing of systemic immunosuppression*		
Good	nd	1 (20.0%)
Moderate	nd	1 (20.0%)
Poor	nd	3 (60.0%)
Sparing of topical steroids		
Taper off	1 (25.0%)	2 (40.0%)
Reduce to ≤ 2 drops / d	0 (0%)	0 (0%)
Unchanged	1 (25.0%)	3 (60.0%)
Increased	2 (50.0%)	0 (0%)

None of the authors has a financial or proprietary interest in any of the material or the method presented.

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Competing Interest

Please list Competing Interests if they exist if not please include the following statement;

Competing Interest: None declared.

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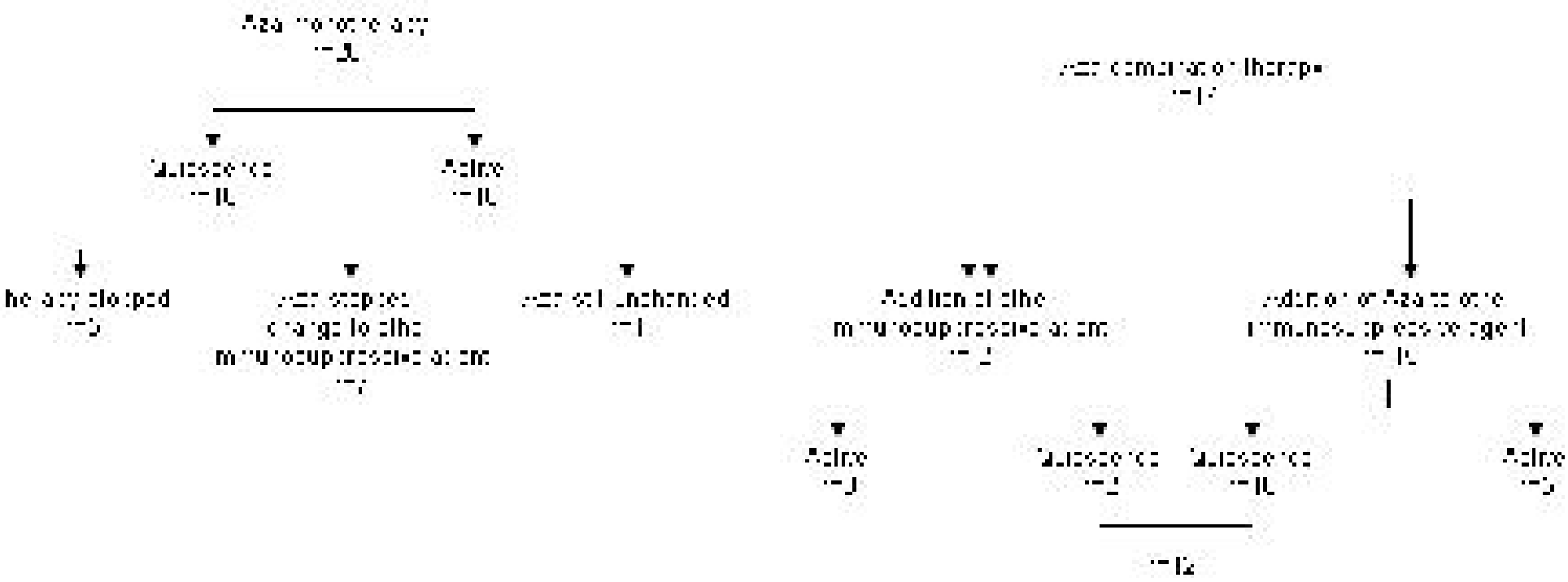
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