

درمان ضایعات چشمی بیماری بهجت

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Rheumatology Research Center

Member: National Elite Foundation – Chair Behcet's Disease

Coordinator: APLAR & Iran WHO-ILAR COPCORD Studies

Chairman: APLAR Special Interest Group on Behcet's Disease

Council Member: International Society for Behcet's Disease

Coordinator: ITR-ICBD

Senior Editor: International Journal of Rheumatic Diseases

Associate Editor: BMC Musculoskeletal Disorders

یازدهمین کنگره سالیانه انجمن روماتولوژی ایران

ضایعات چشمی

Ben Ezra D, British J Ophthalmol 1986; 70: 589-592

با اینکه ضایعات چشمی بیماری بهجت را ما از نزدیک
مراقب هستیم و سنگین درمان مینماییم ، متاسفانه ۶ تا ۱۰
سال بعد از شروع ضایعات ، ۷۴ در صد چشمهای درگیر دید
مفید خود را از دست میدهند (کوری قانونی).

یازدهمین کنگره سالیانه انجمن روماتولوژی ایران

داروها

خط اول درمان

- داروهای سایتو توکسیک
- همراه با پردنیزولون
- نیم میلیگرم بر حسب کیلوگرم وزن بدن
- بصورت دوز منقسم (حد اقل ۲ دوز در روز)

برای درمان ضایعات چشمی بهجت

- دارو ، نه تنها باید موثر باشد
- باید عوارض جانبی قابل قبول و با شیوع کم داشته باشد
- باید تاثیر پذیری خود را بمدت طولانی حفظ نماید
- نه فقط برای چند ماه یا چند سال
- بلکه برای چندین و چند سال
- و بالاخره ، باید مخارج آن سنگین نبوده و قابل پرداخت باشد
- سایتو توکسیک ها تمام شرایط فوق را دارند

لیست داروهای سایتوتوکسیک

- Chlorambucil
- Cyclosporine
- Methotrexate
- Azathioprine
- Pulse Cyclophosphamide
- PCP – MTX
- PCP – AZA

CHLORAMBUCIL

CHLORAMBUCIL

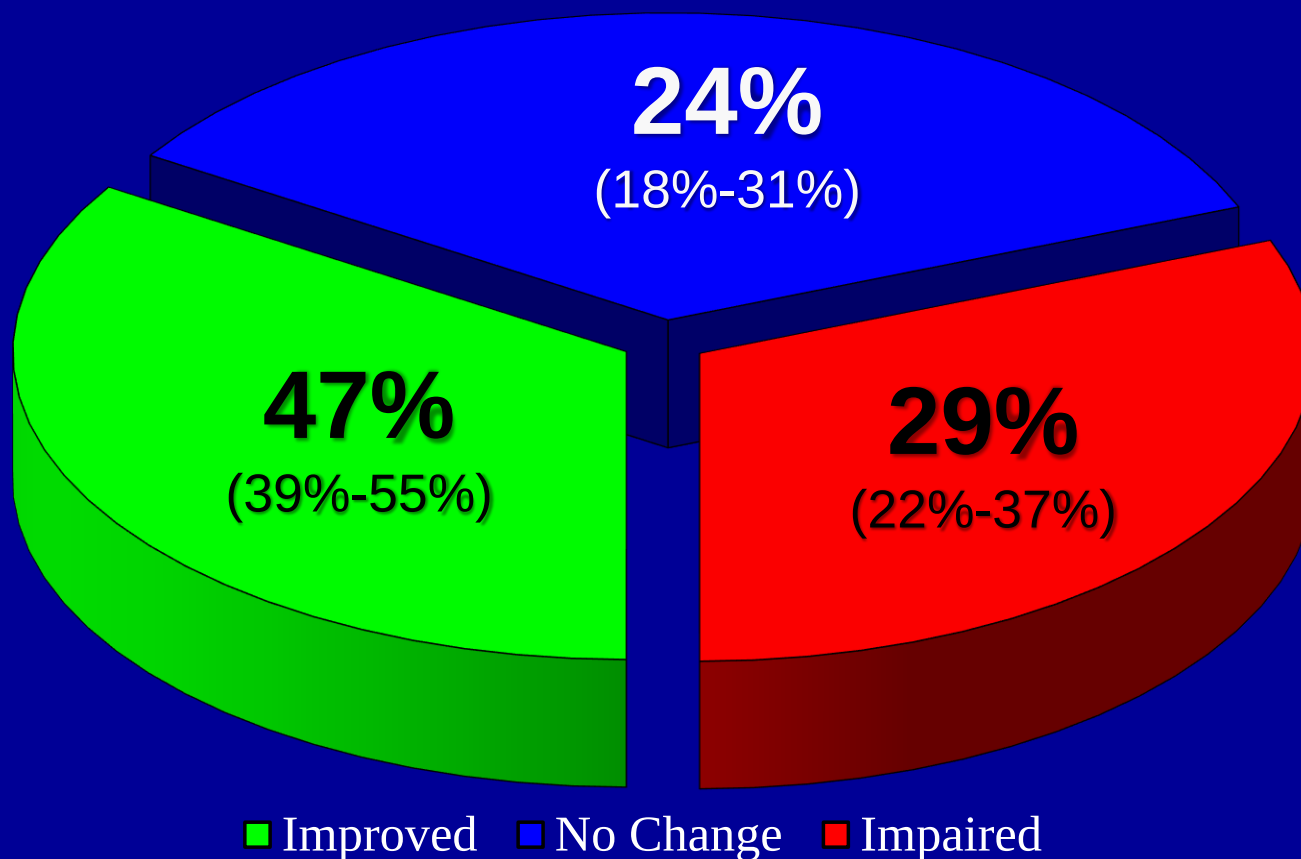
89 Patients

Longitudinal Study up to 15 Years

788 Eyes-Years Follow-Up

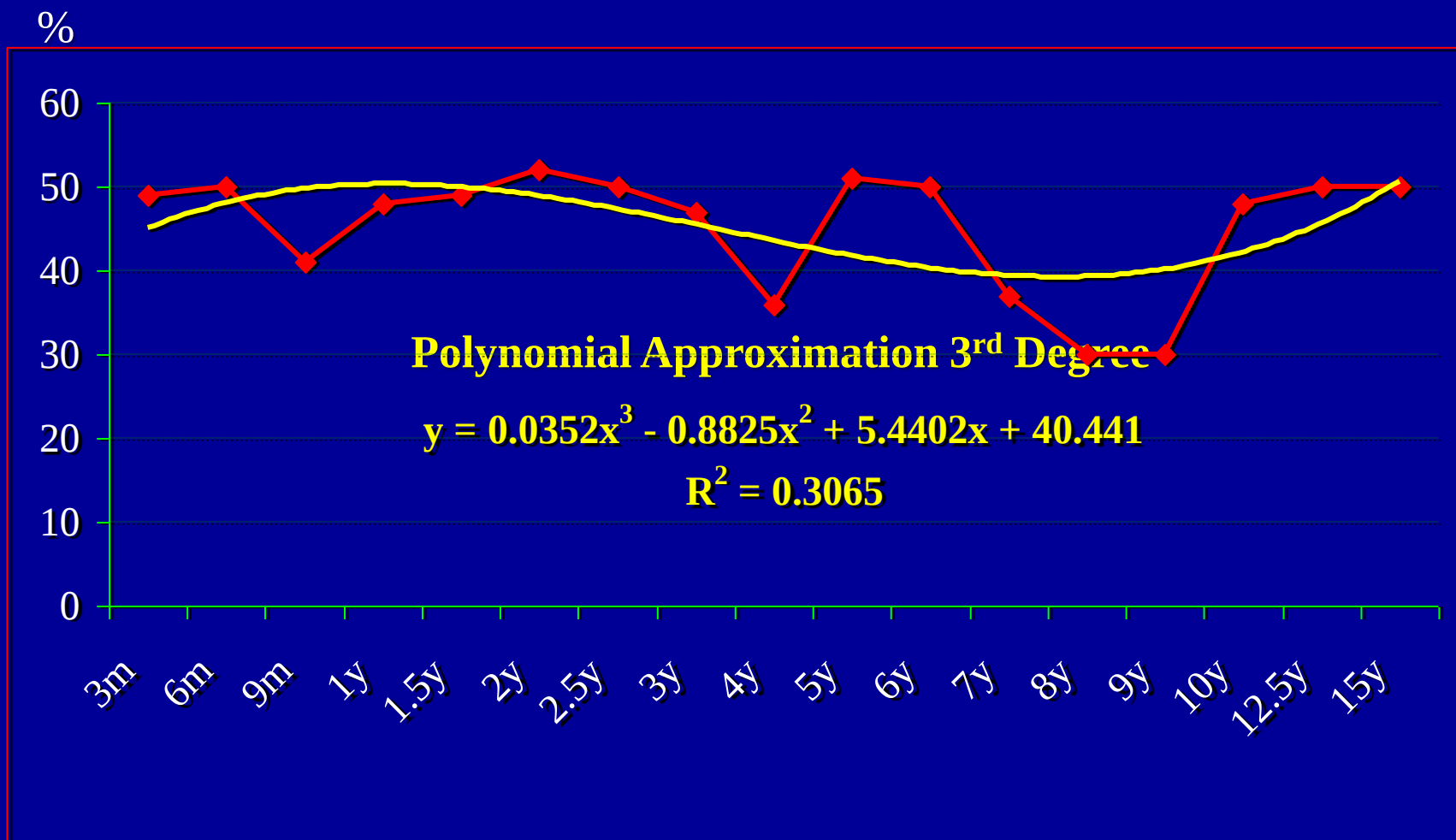
VISUAL ACUITY

CHL



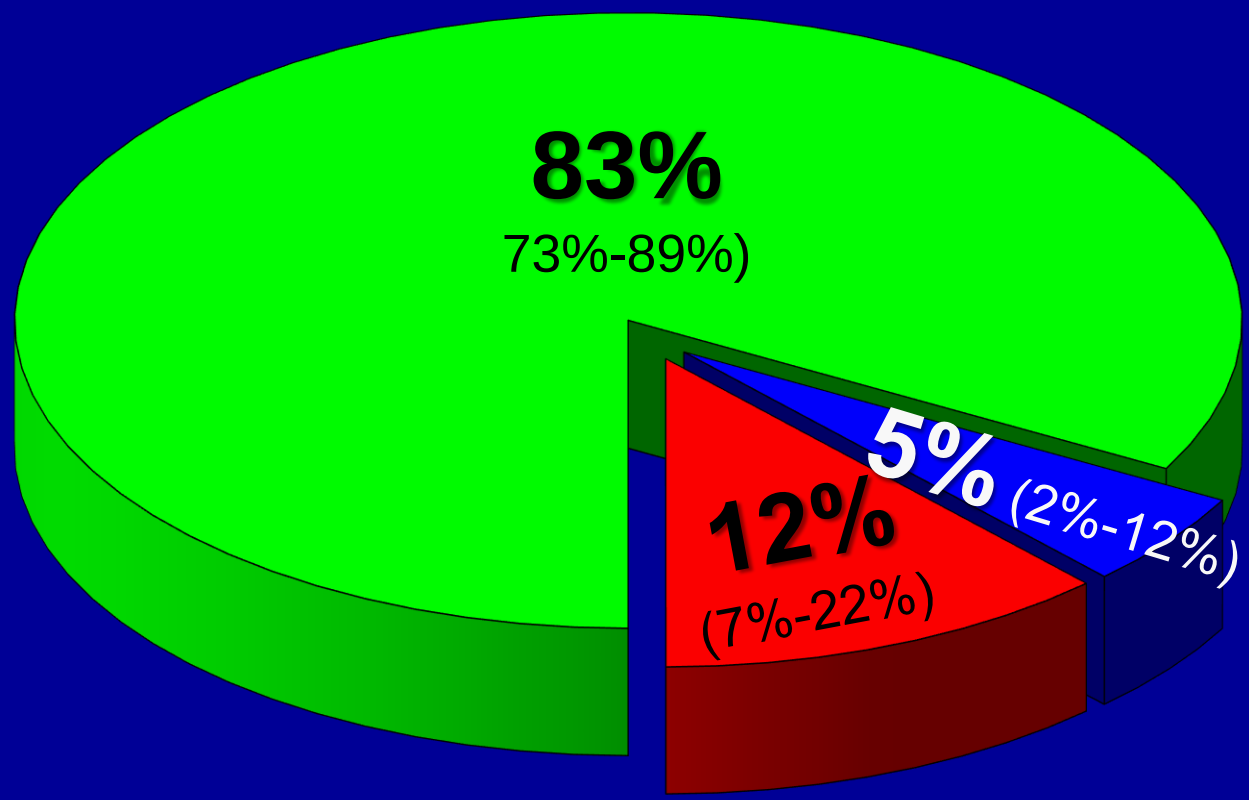
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

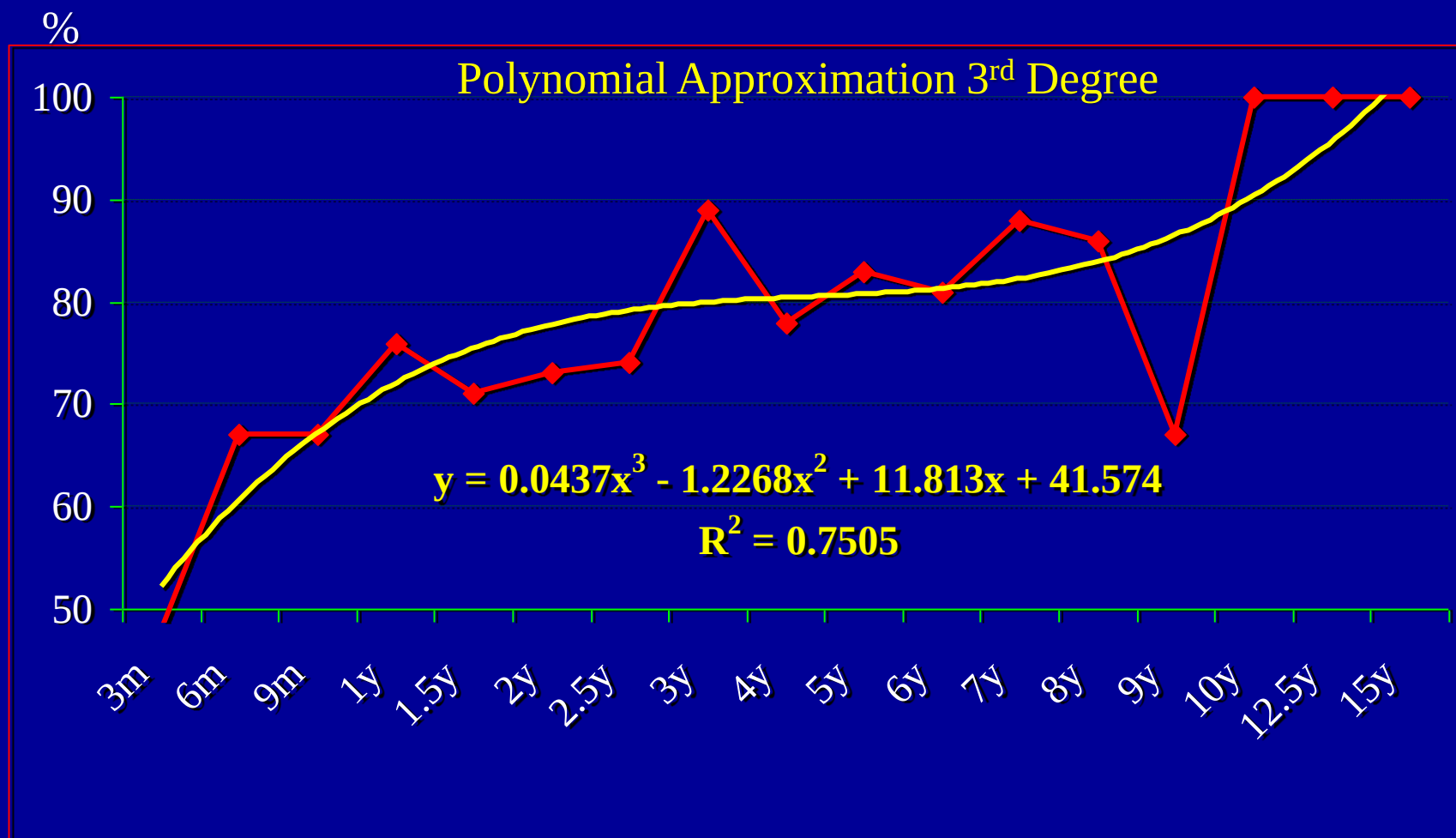
CHL



■ Improved ■ No Change ■ Impaired

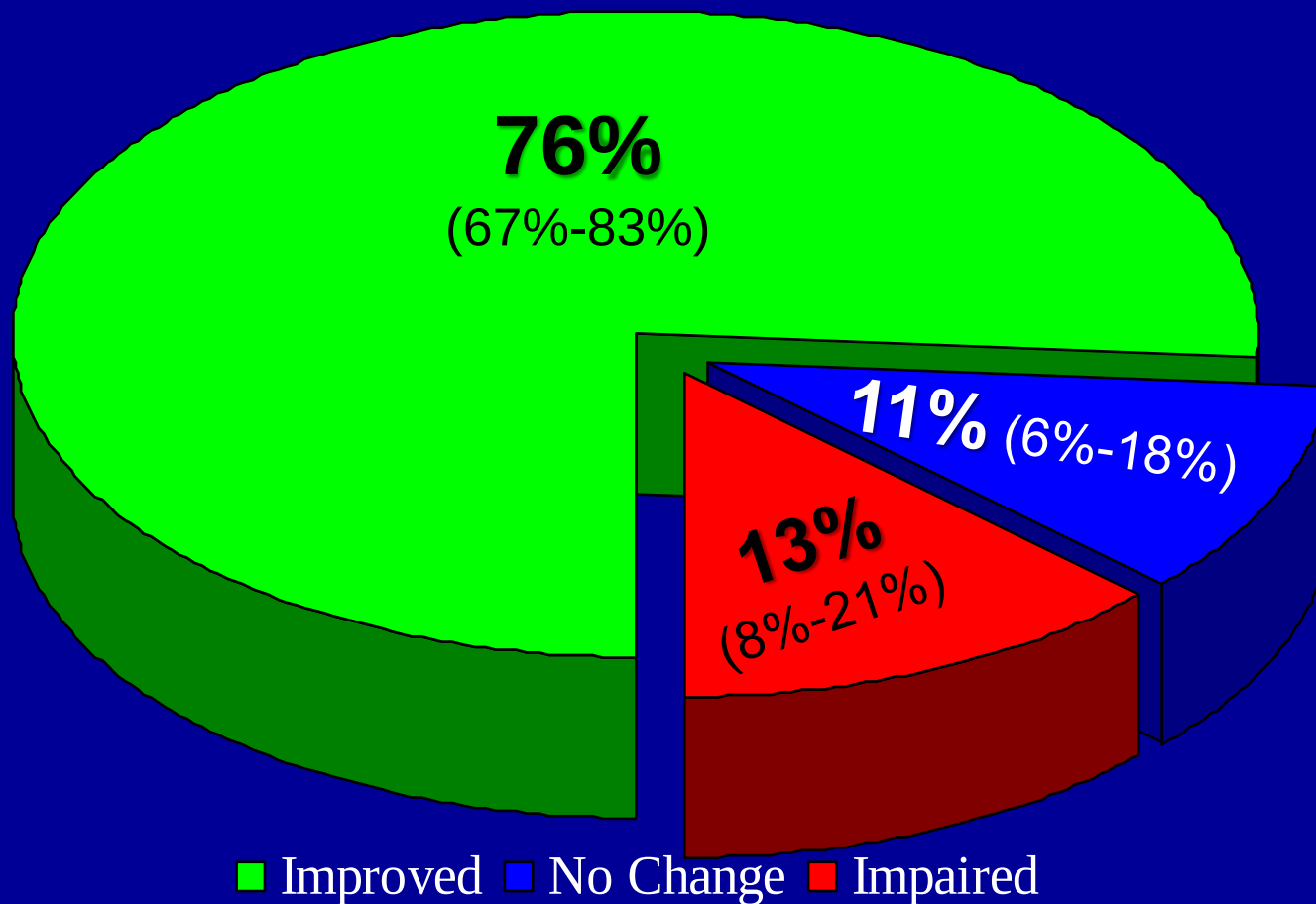
Longitudinal Study

Anterior Uveitis – % Improvement



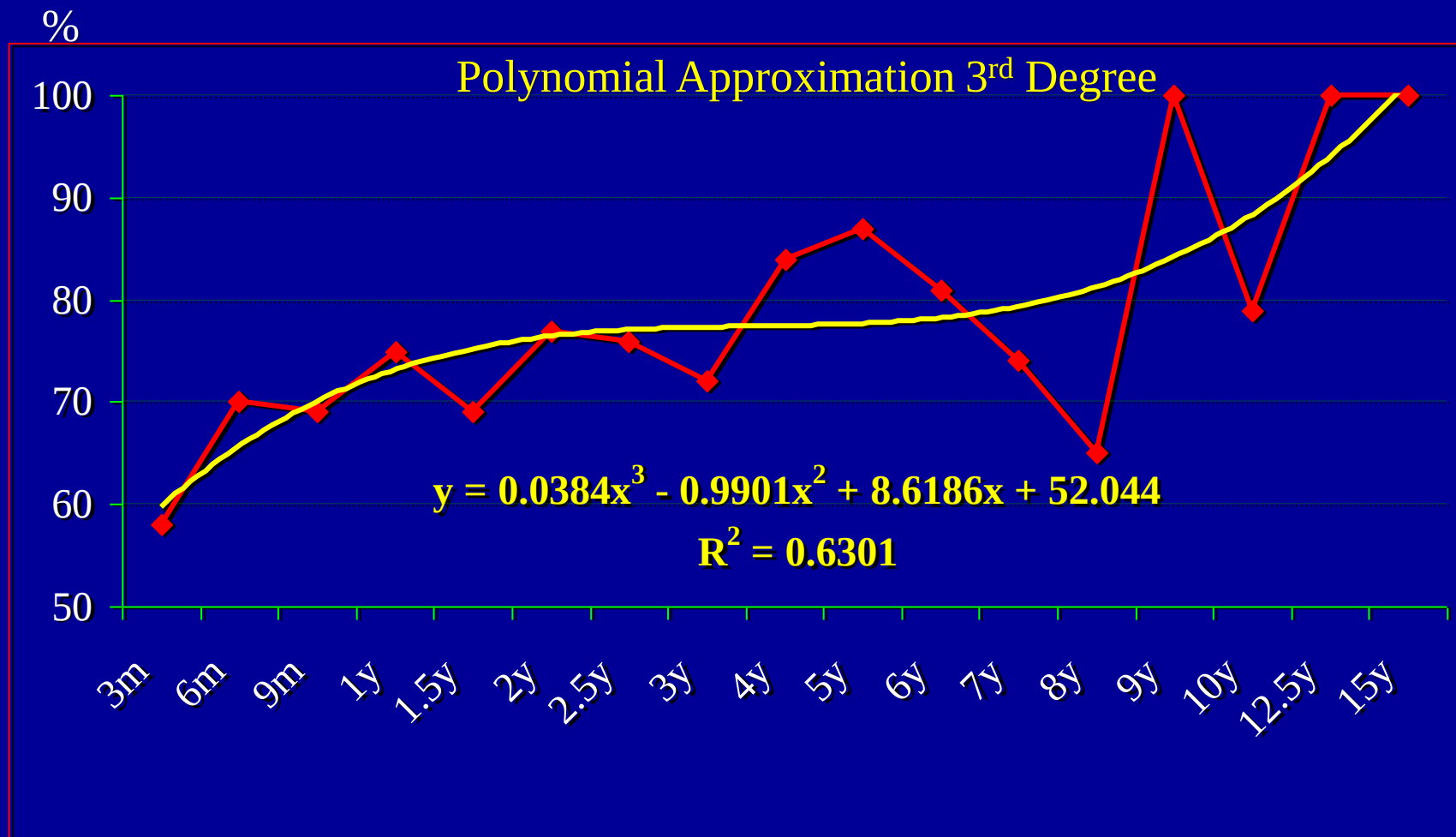
POSTERIOR UVEITIS

CHL



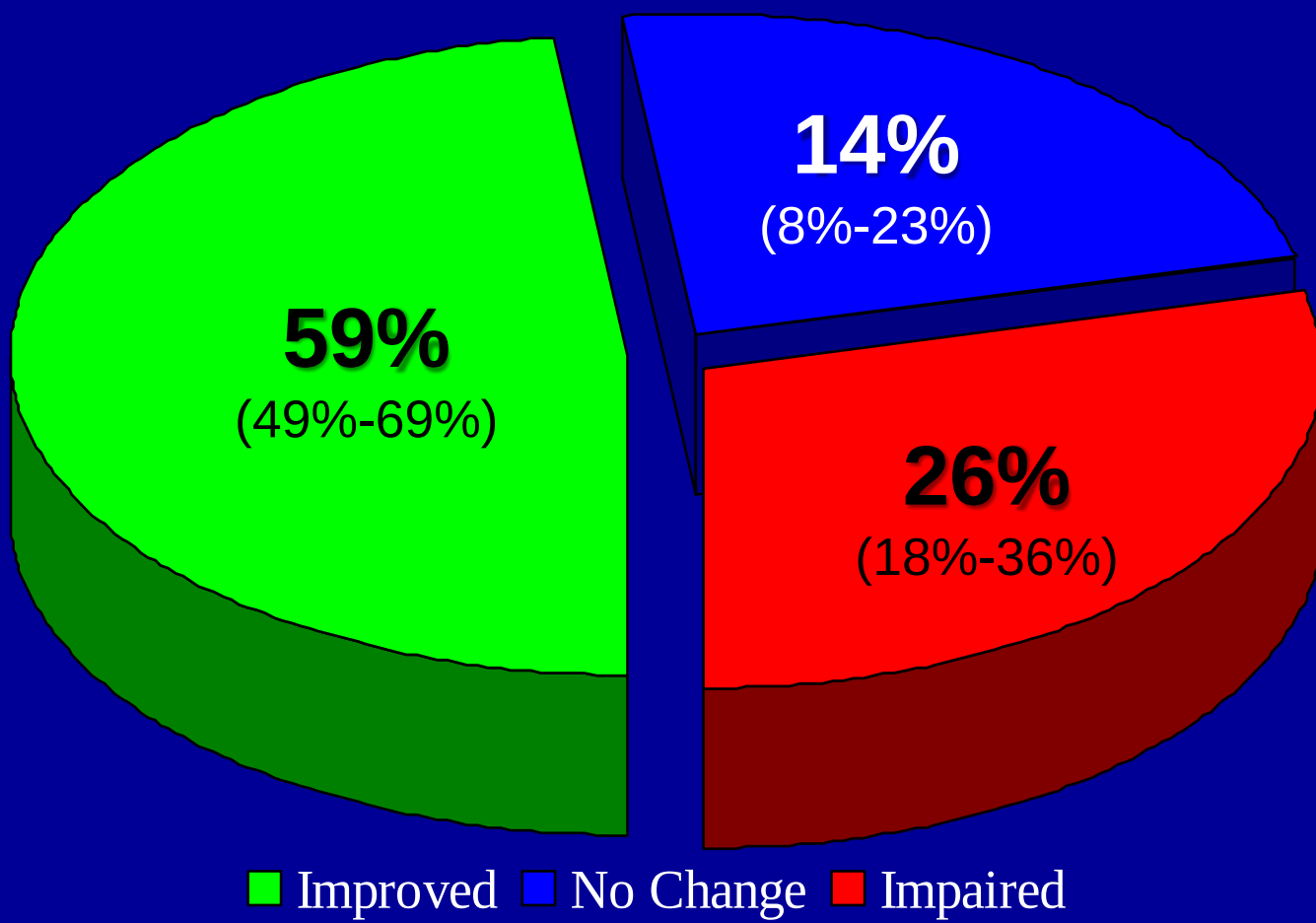
Longitudinal Study

Posterior Uveitis – % Improvement



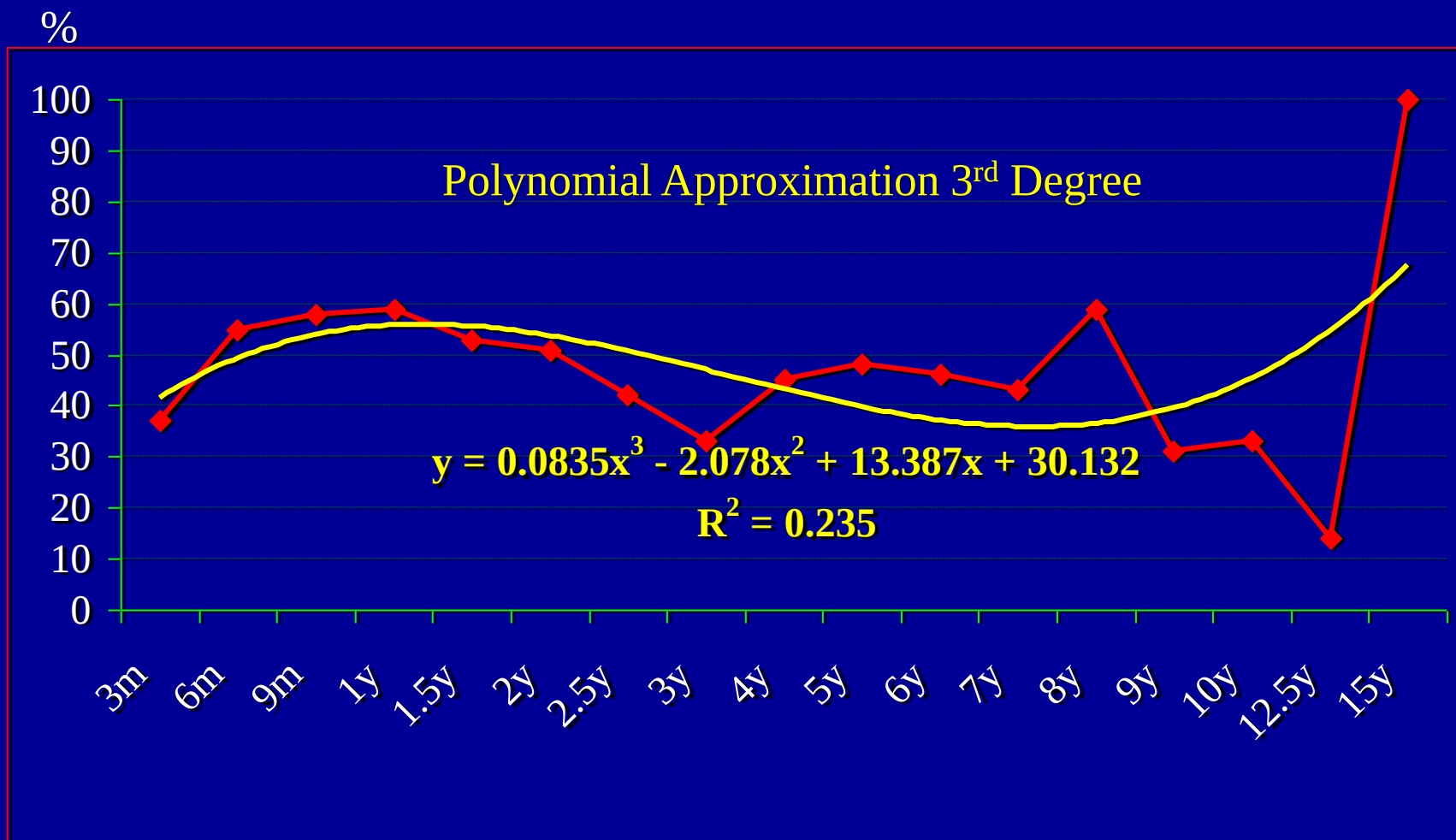
RETINAL VASCULITIS

CHL



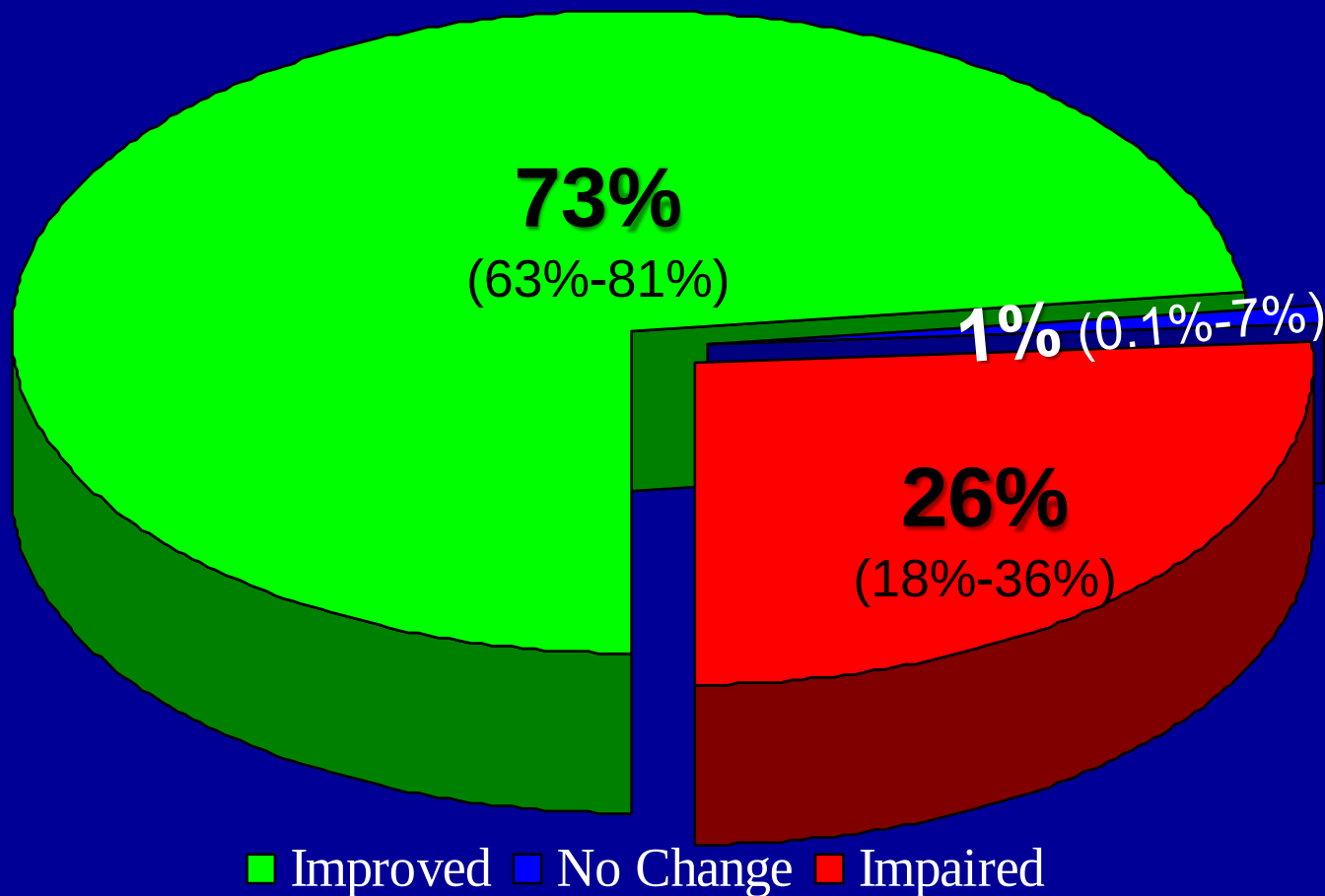
Longitudinal Study

Retinal Vasculitis – % Improvement



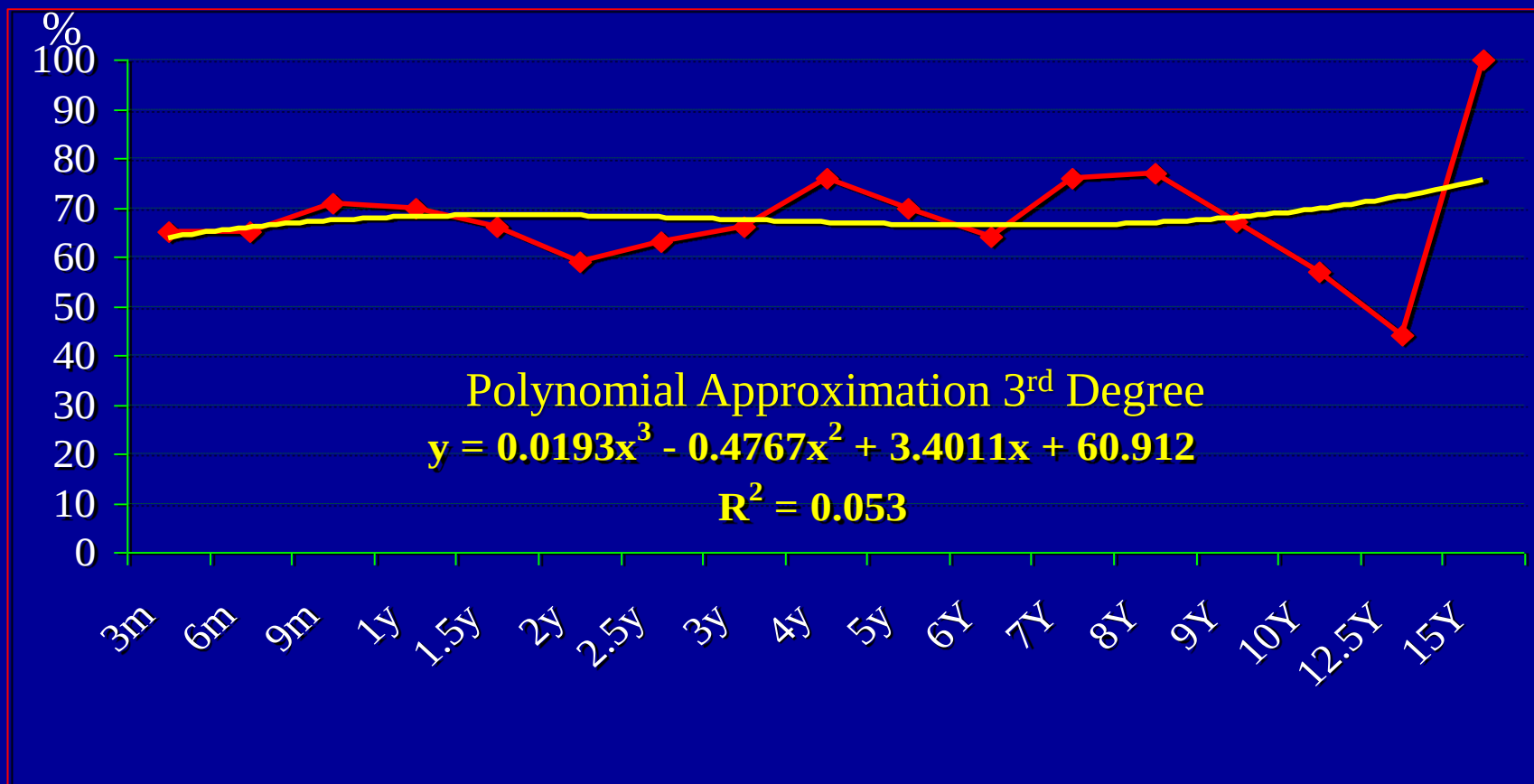
TOTAL ADJUSTED DISEASE ACTIVITY INDEX

$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$



Longitudinal Study

$T_{\text{otal}} A_{\text{djusted}} D_{\text{isease}} A_{\text{ctivity}} I_{\text{ndex}} - \% \text{ Improvement}$



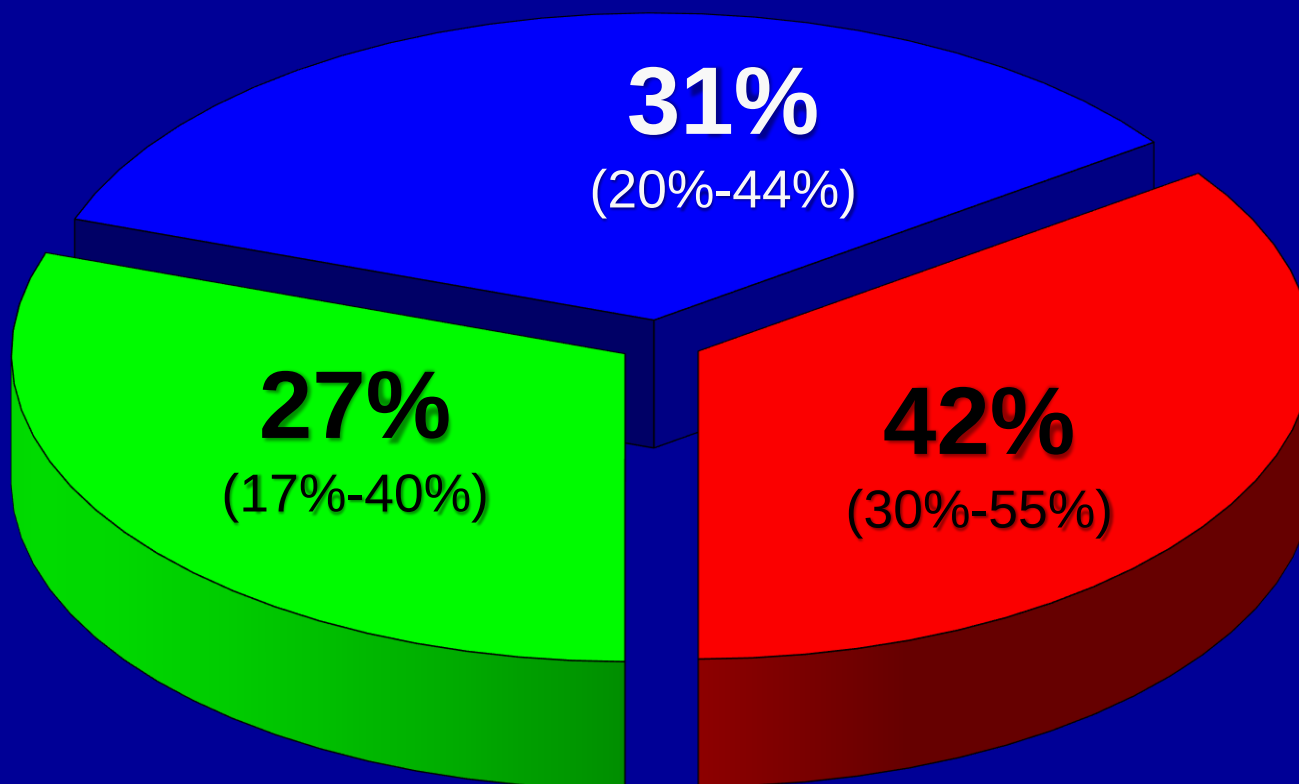
CYCLOSPORINE

37 Patients

Longitudinal Study up to 20 Years

VISUAL ACUITY

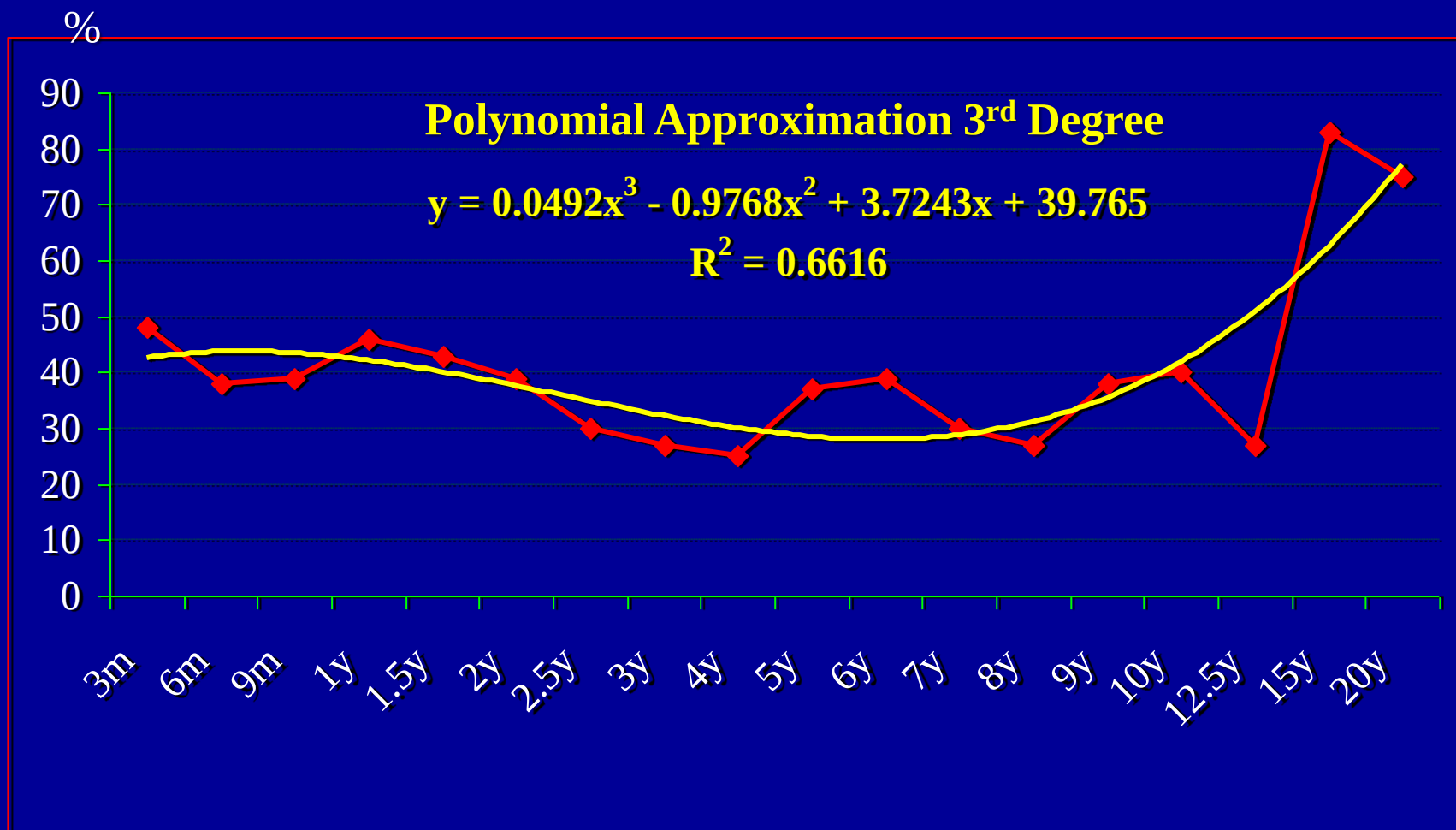
Cycle



■ Improved ■ No Change ■ Impaired

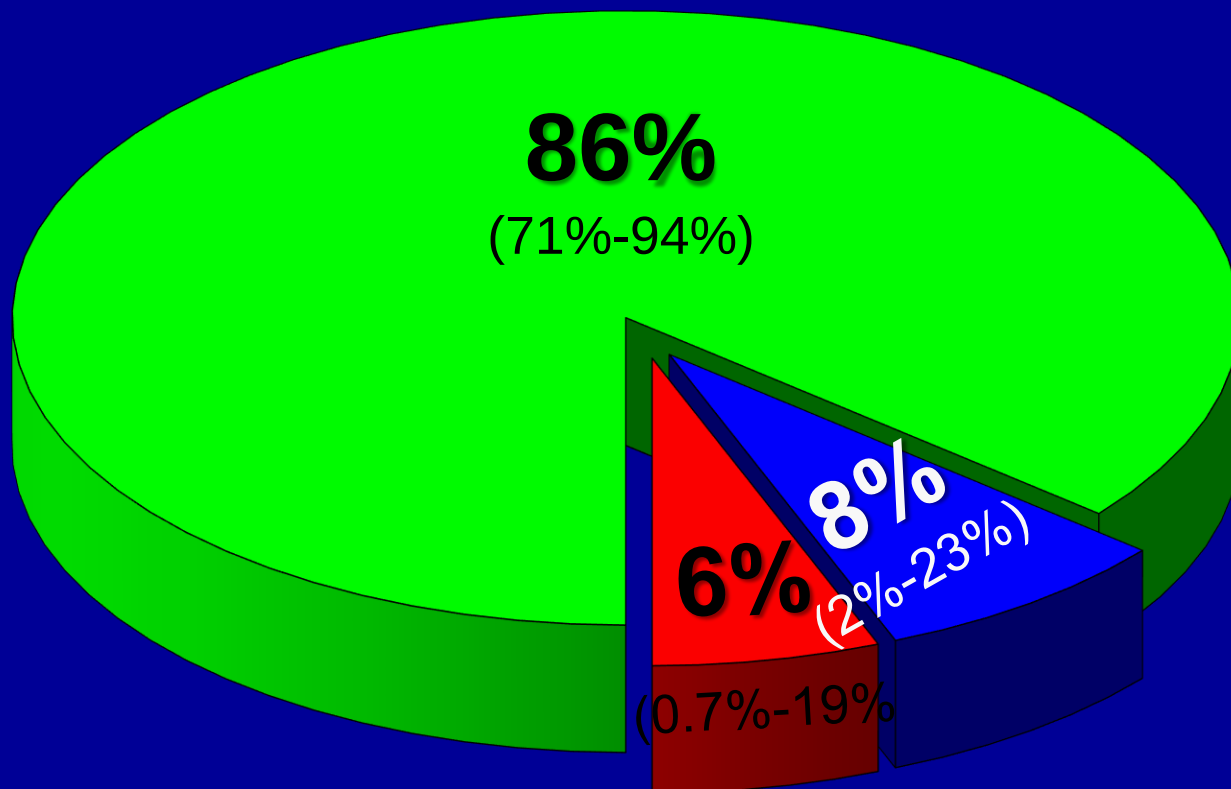
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

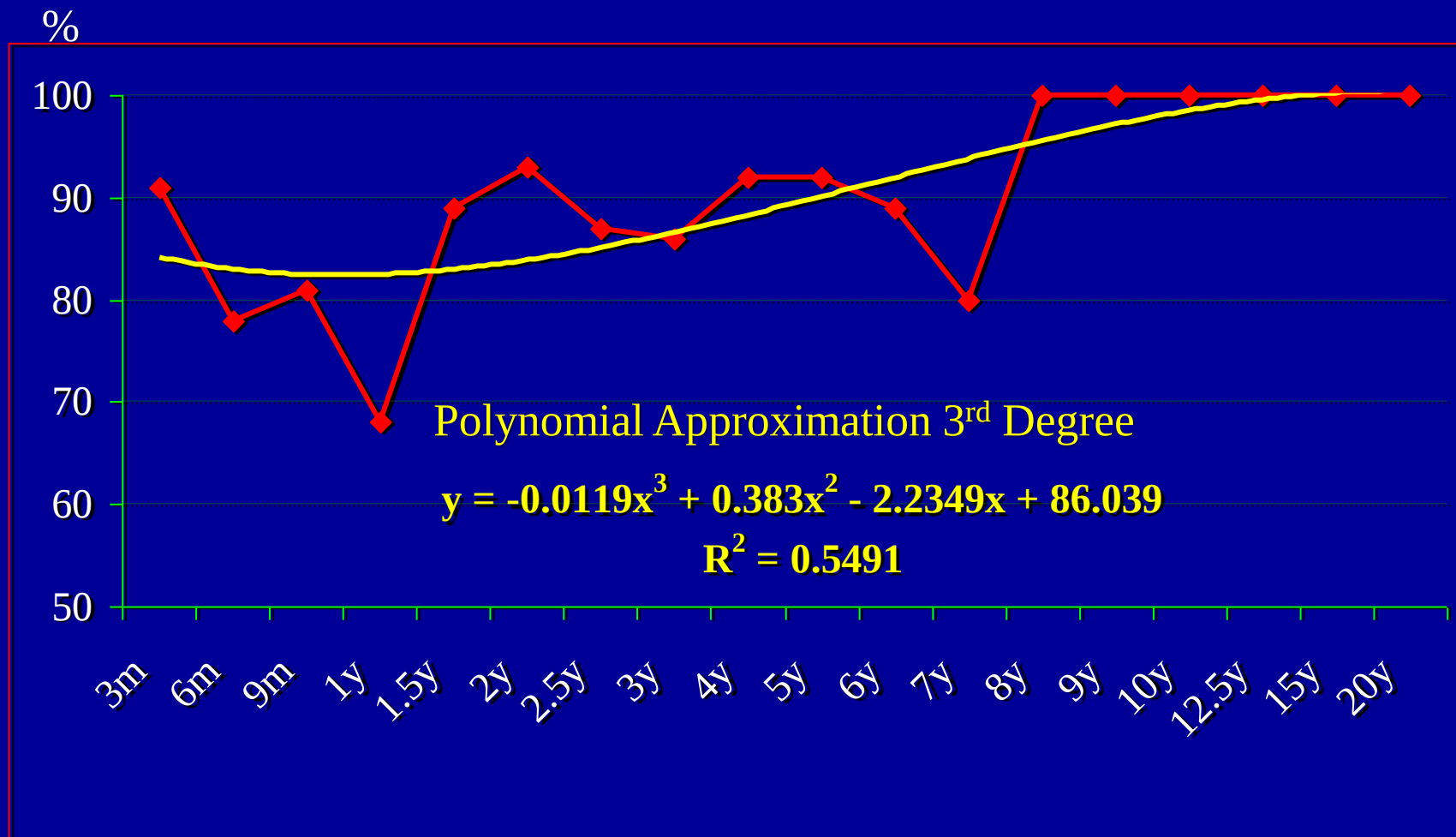
Cyclo



■ Improved ■ No Change ■ Impaired

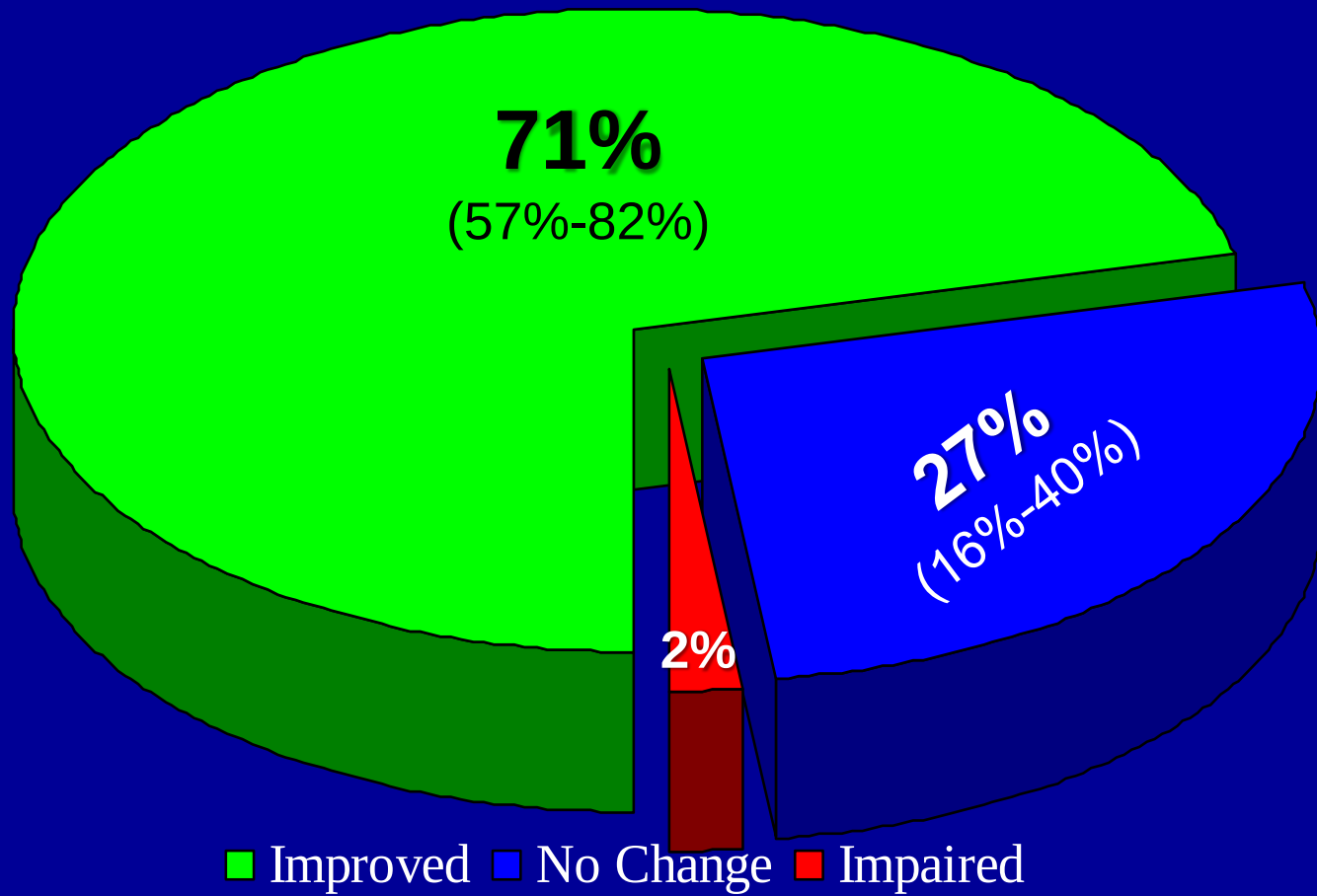
Longitudinal Study

Anterior Uveitis – % Improvement



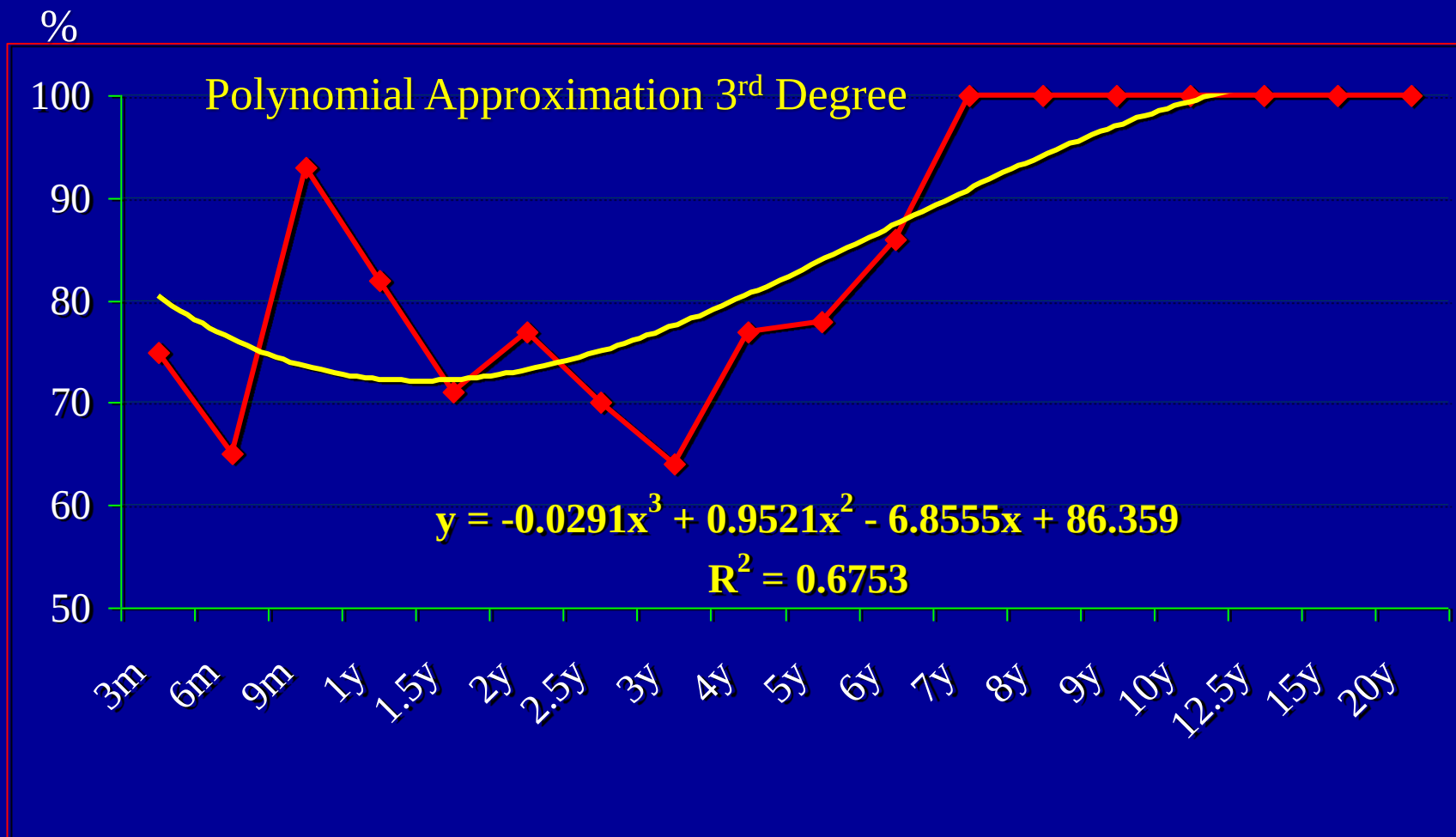
POSTERIOR UVEITIS

Cyclo



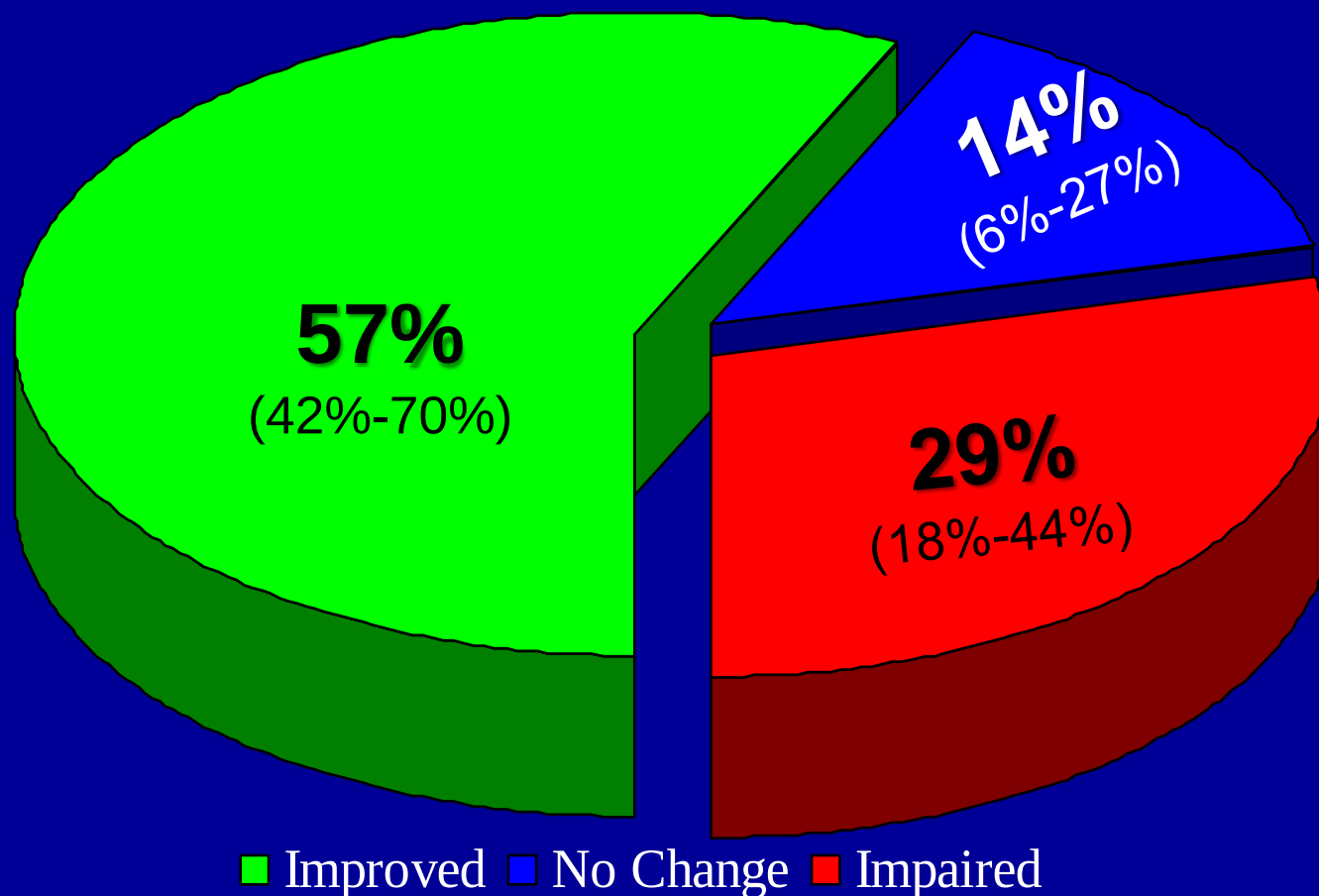
Longitudinal Study

Posterior Uveitis – % Improvement



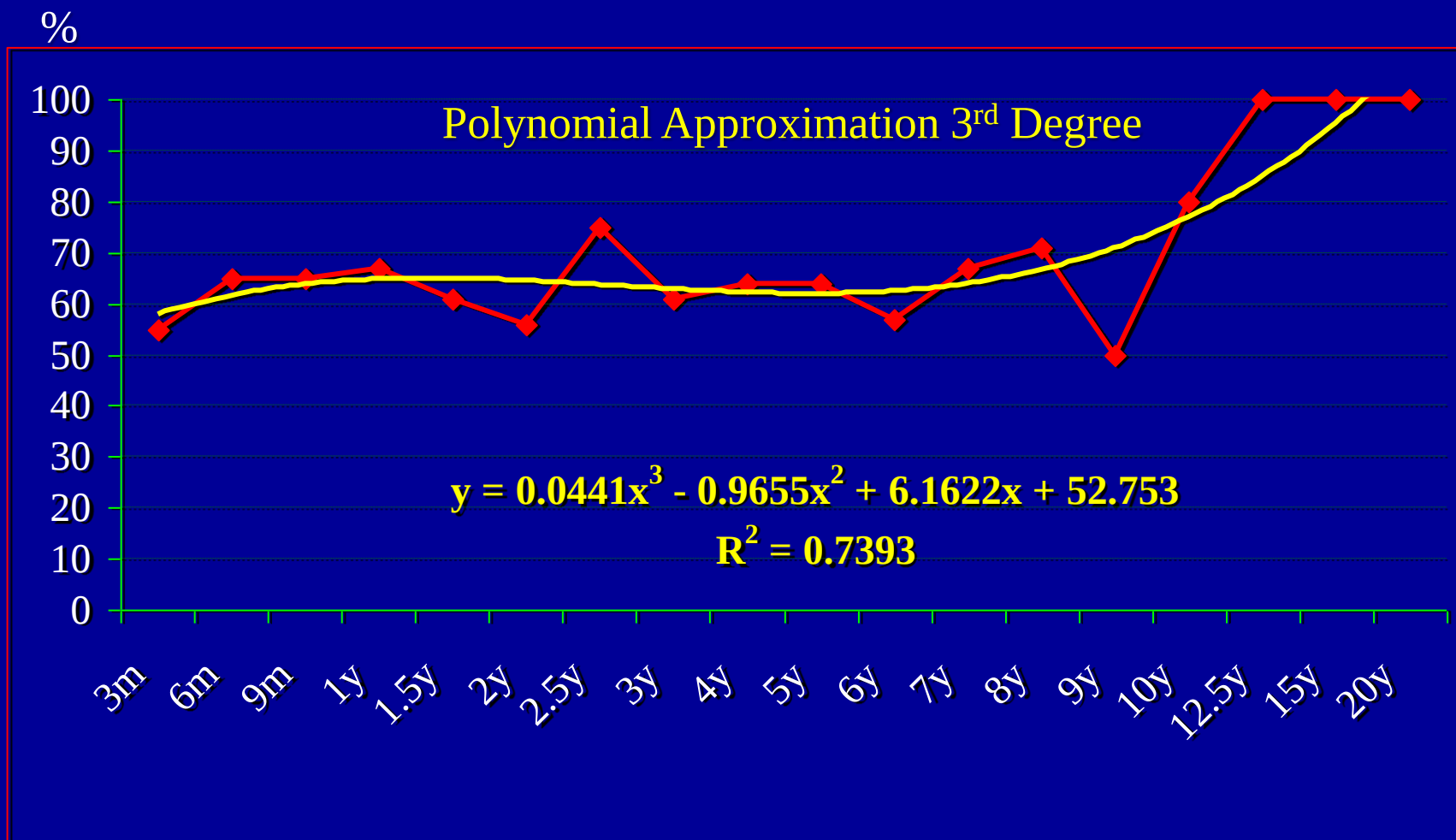
RETINAL VASCULITIS

Cyclo



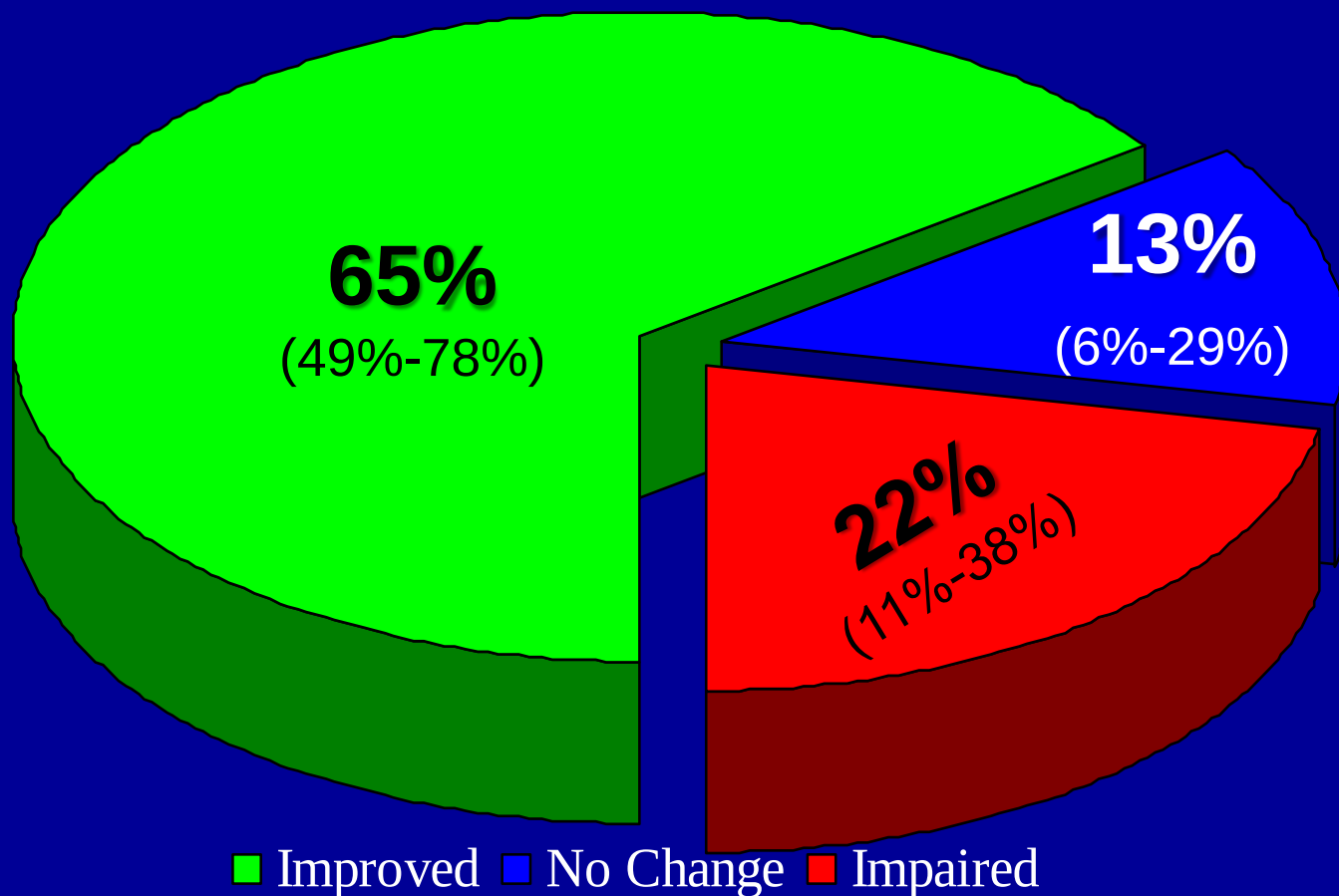
Longitudinal Study

Retinal Vasculitis – % Improvement



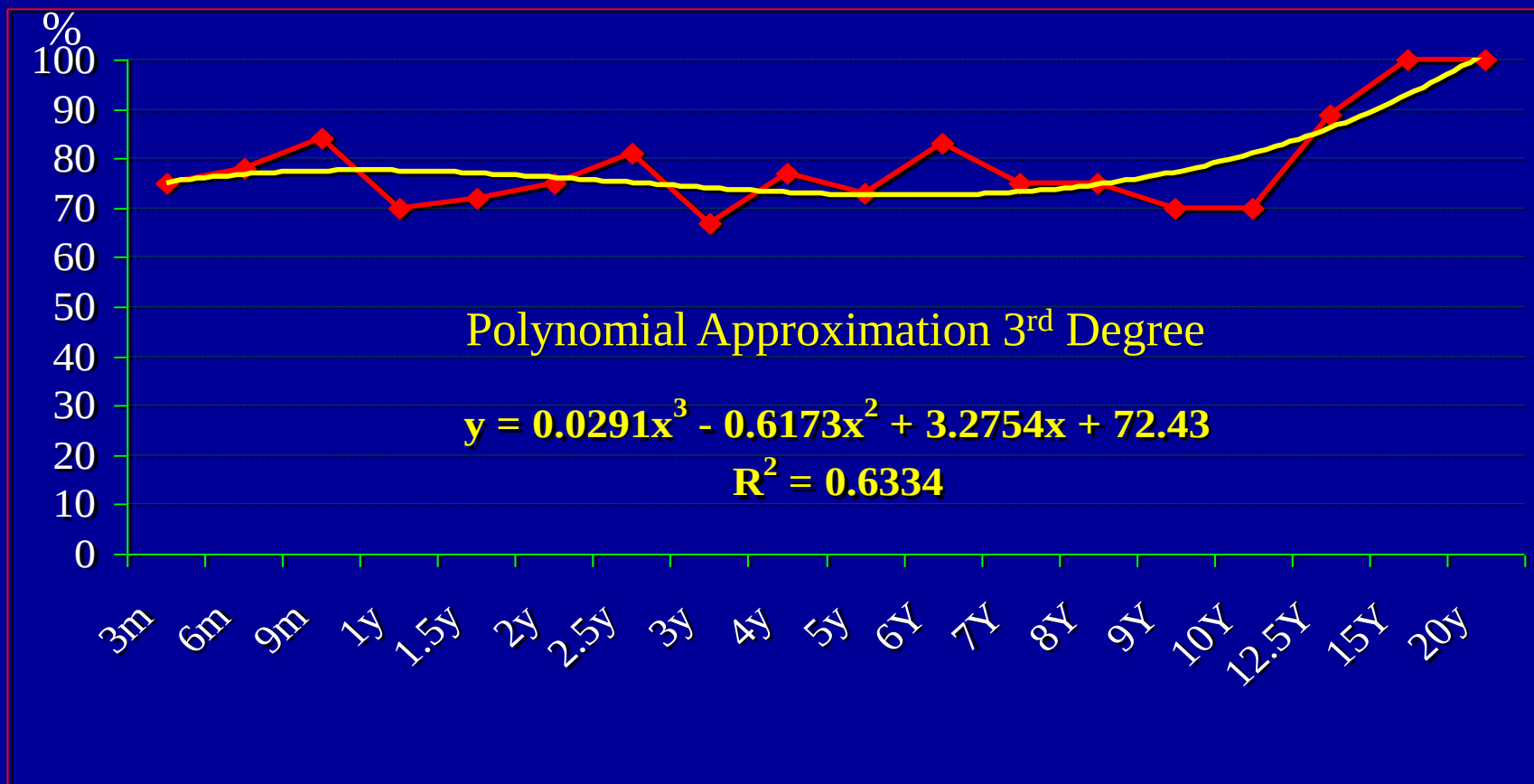
TOTAL ADJUSTED DISEASE ACTIVITY INDEX

$$\frac{(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]}{\text{Cyclo}}$$



Longitudinal Study

T_{total} A_{adjusted} D_{disease} A_{activity} I_{index} — % Improvement



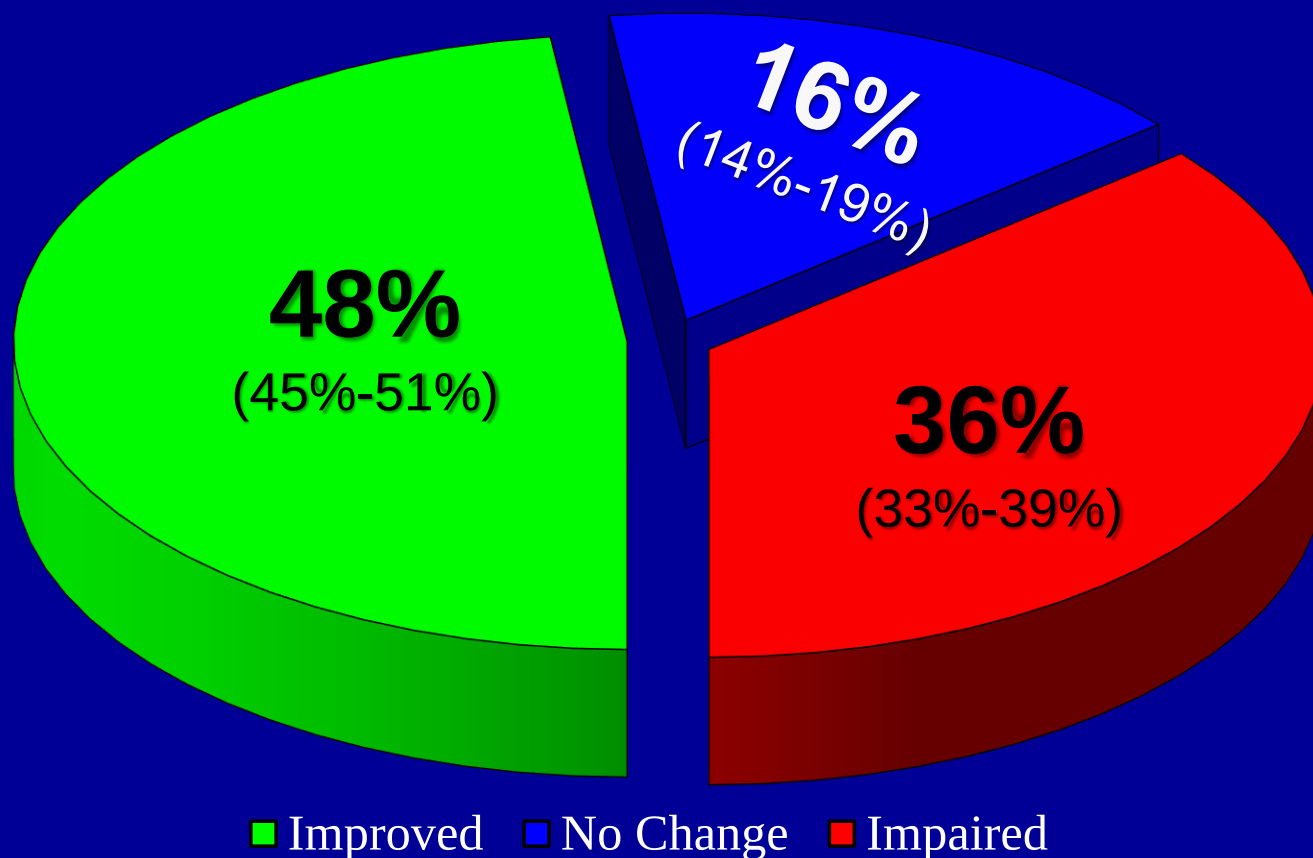
METHOTREXATE

787 Patients

Longitudinal Study up to 20 Years

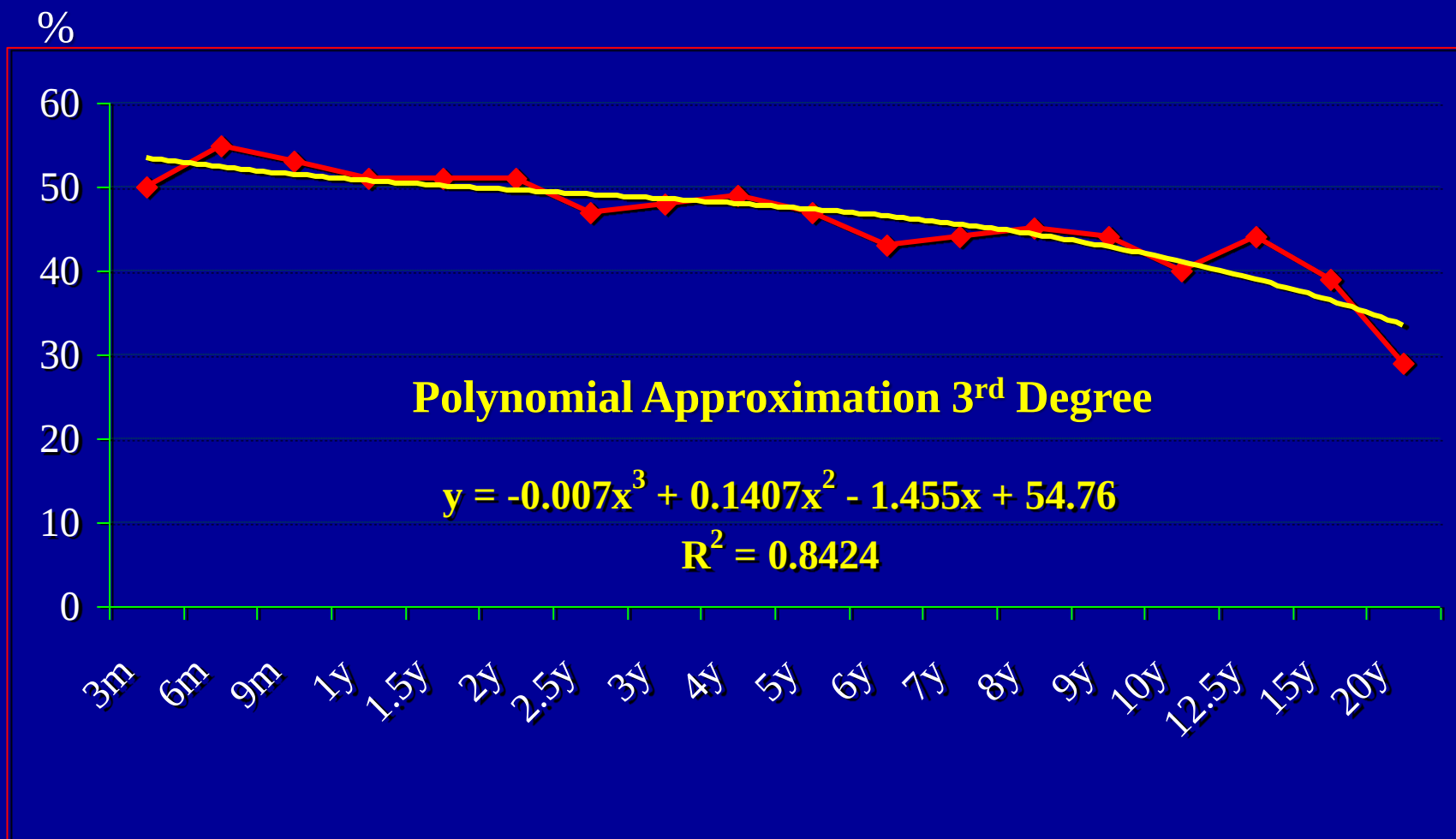
VISUAL ACUITY

MTX



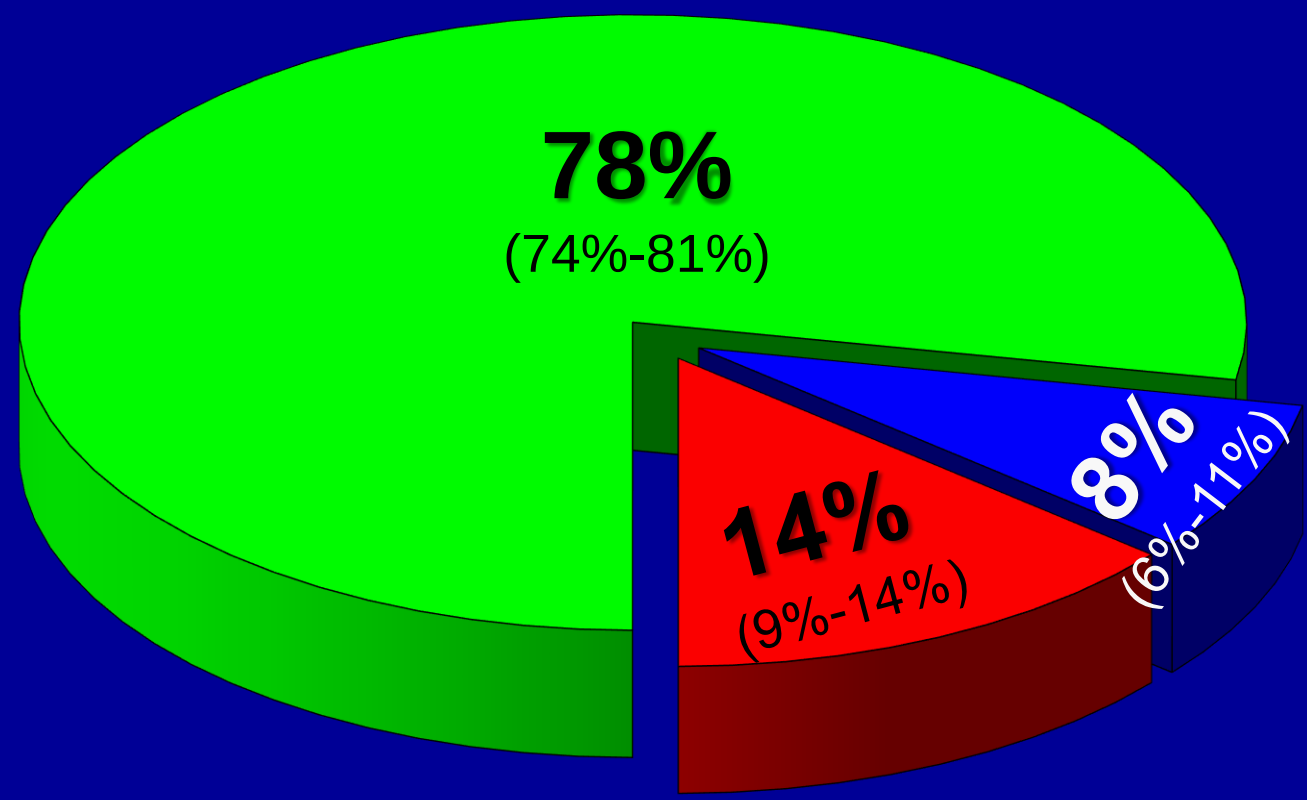
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

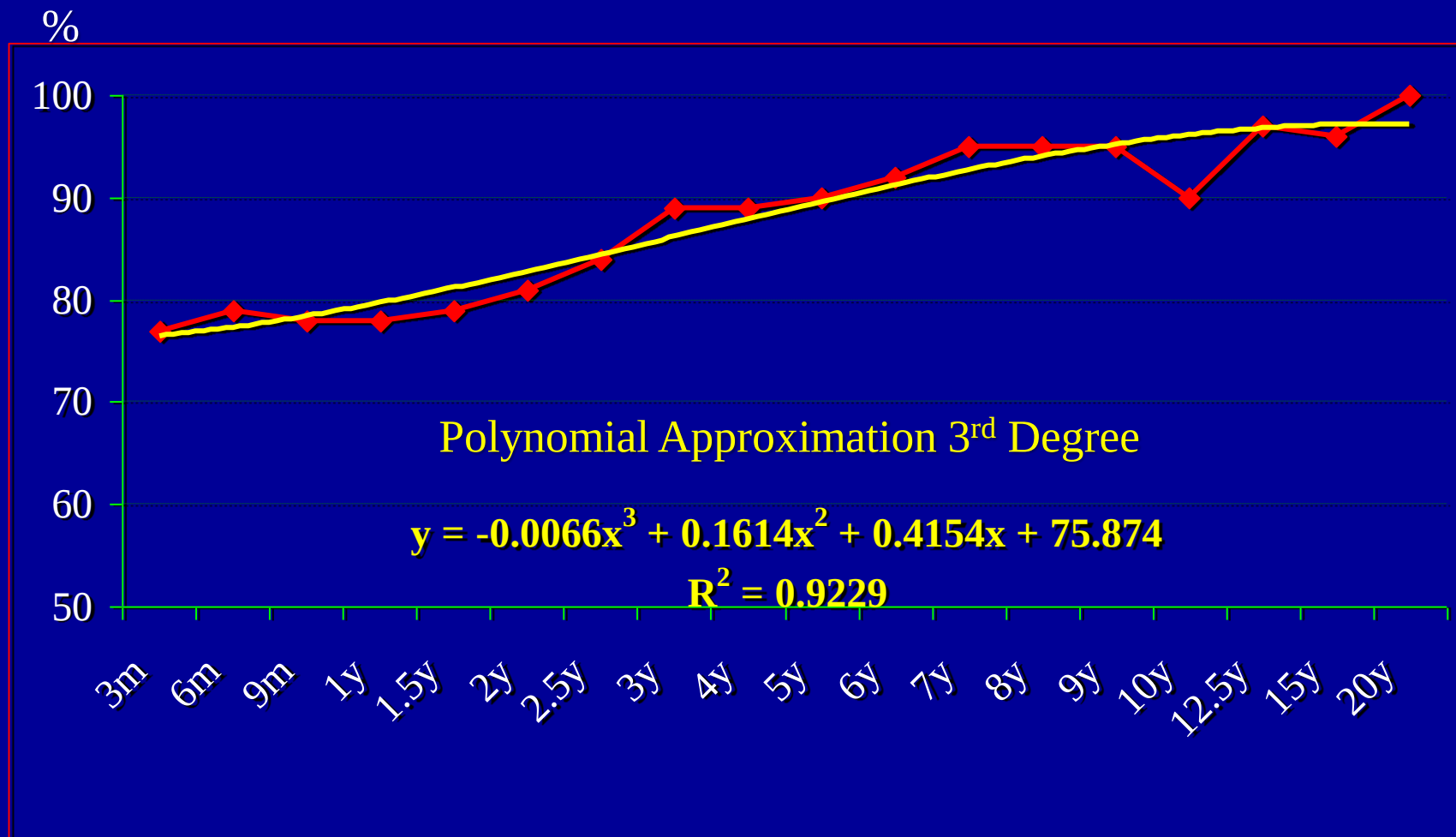
MTX



■ Improved ■ No Change ■ Impaired

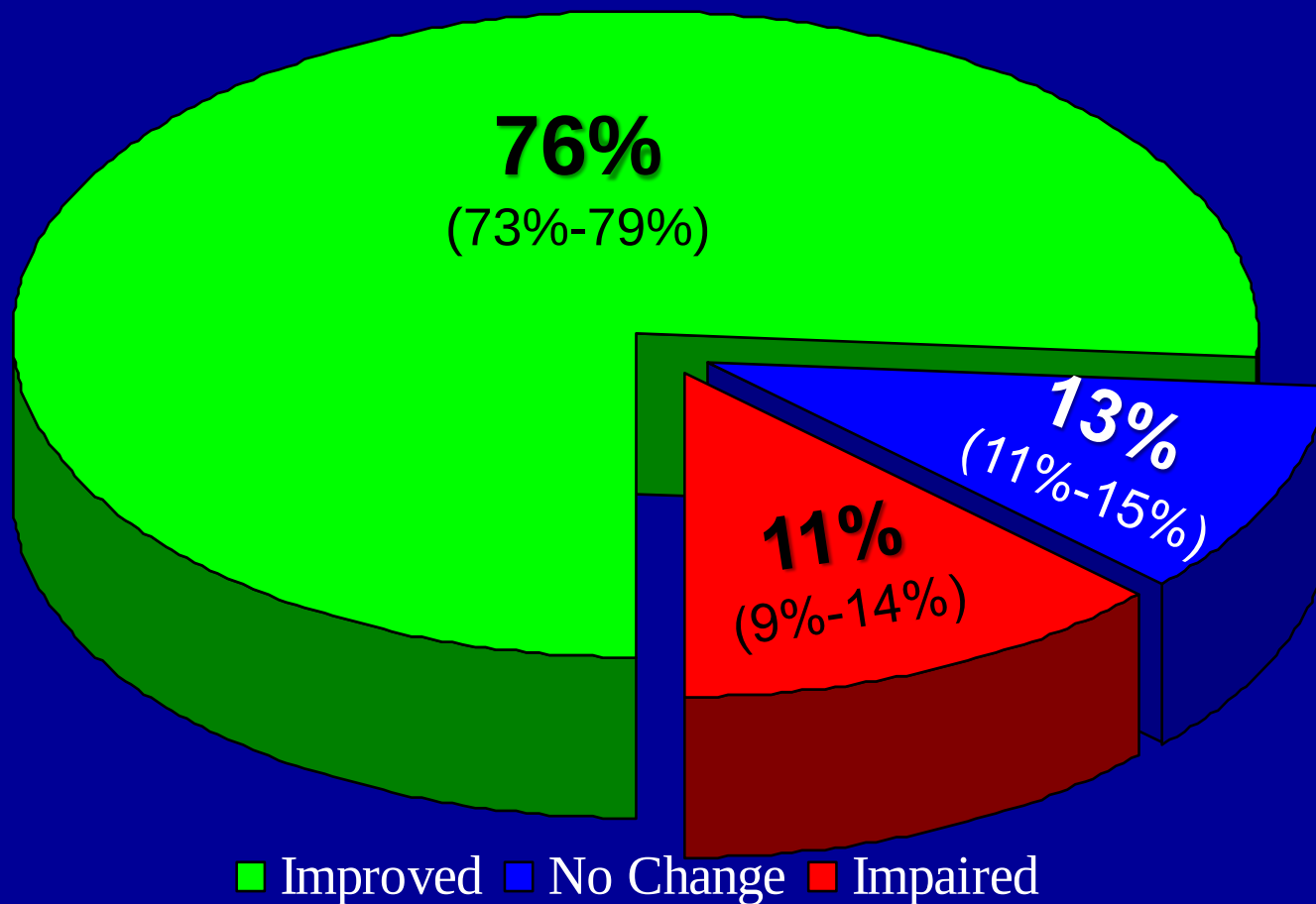
Longitudinal Study

Anterior Uveitis – % Improvement



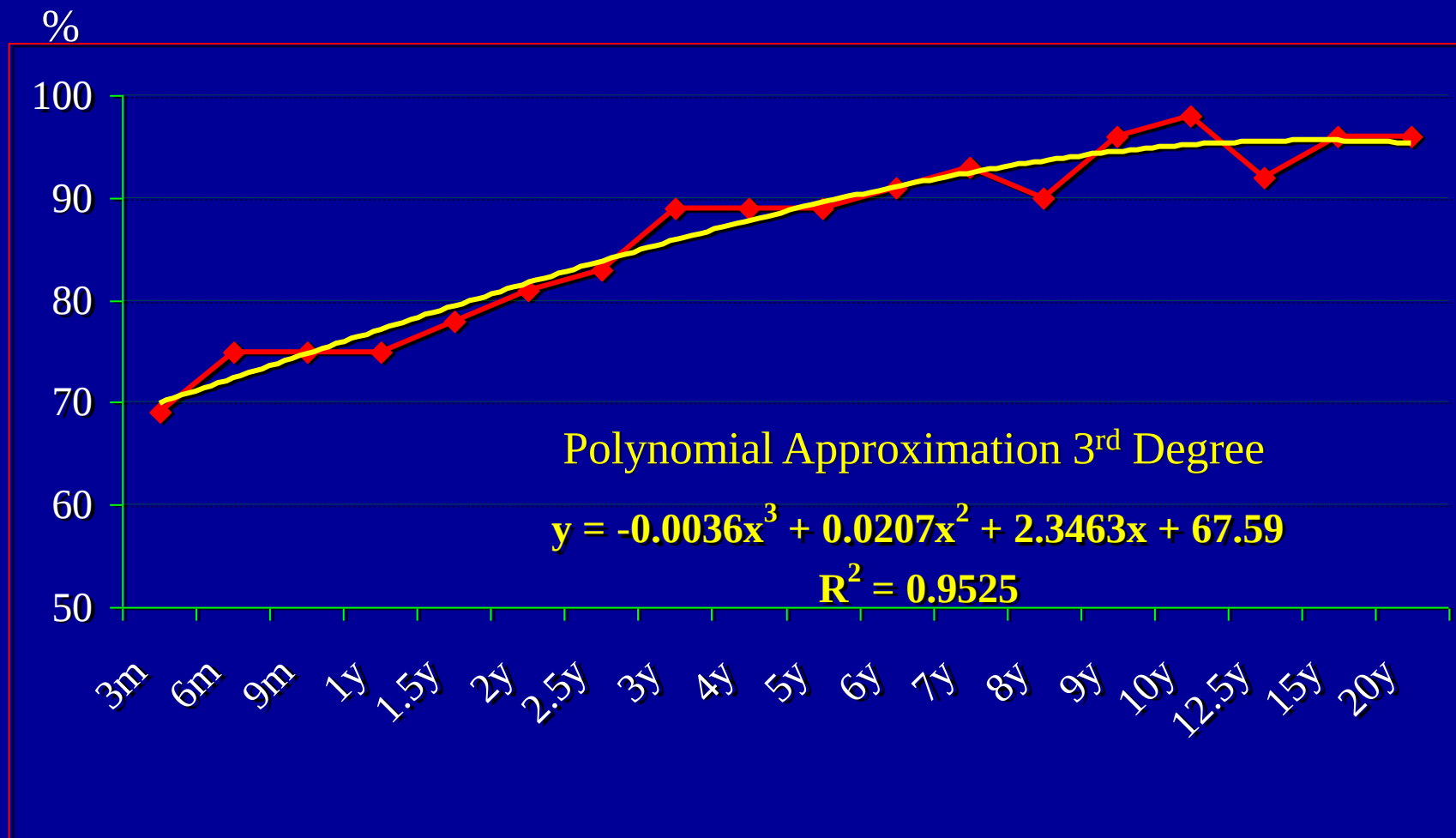
POSTERIOR UVEITIS

MTX



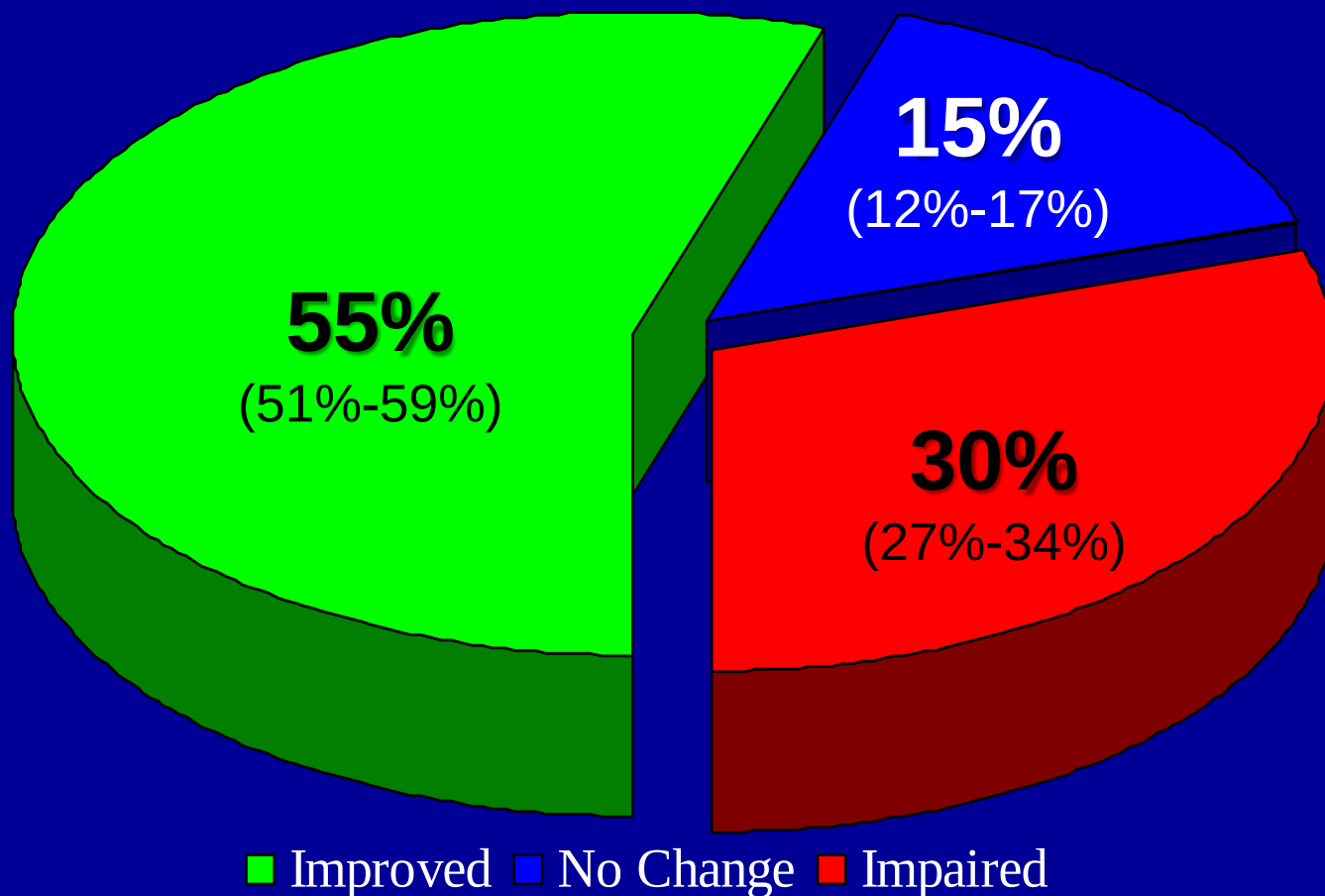
Longitudinal Study

Posterior Uveitis – % Improvement



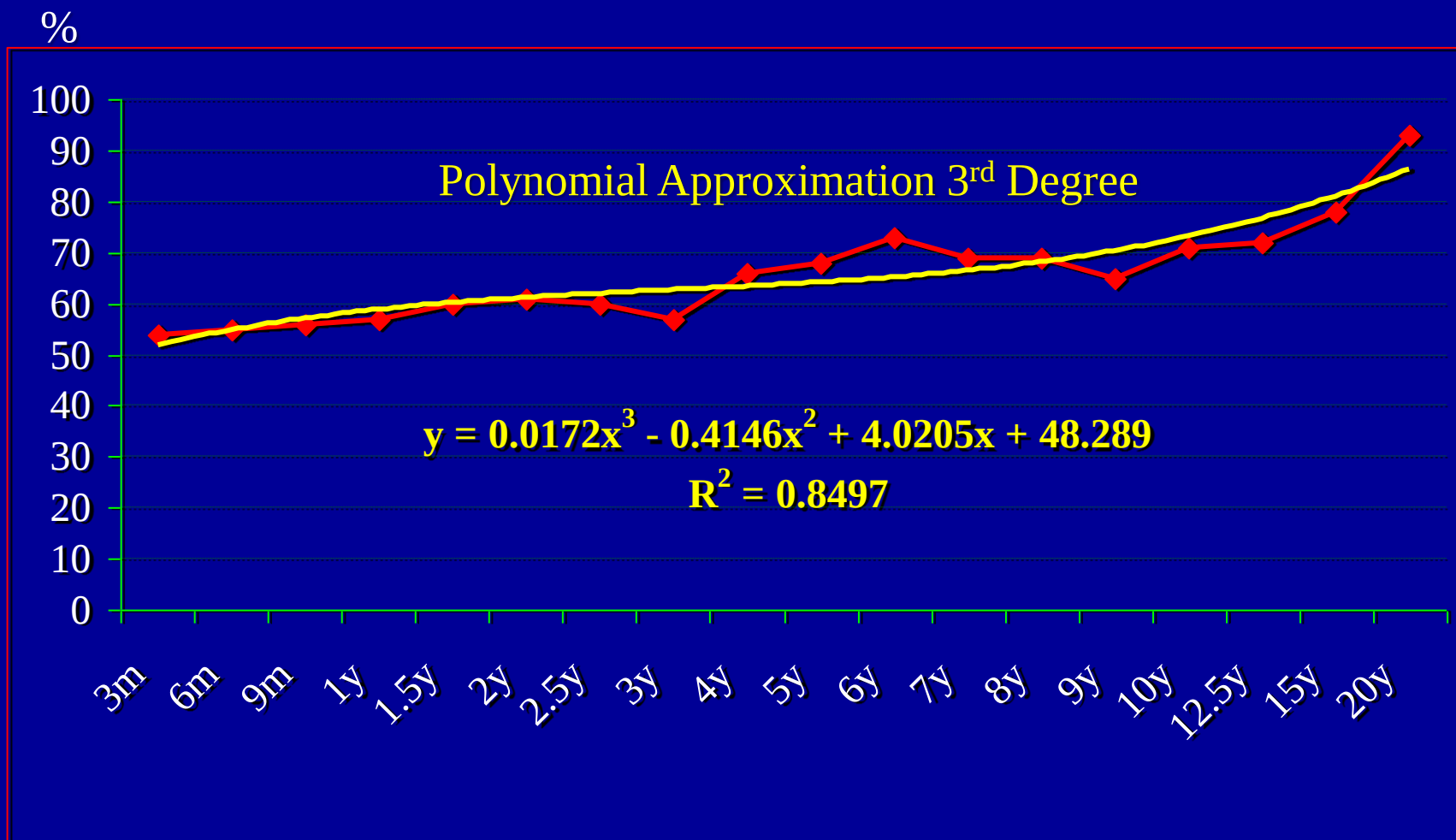
RETINAL VASCULITIS

MTX



Longitudinal Study

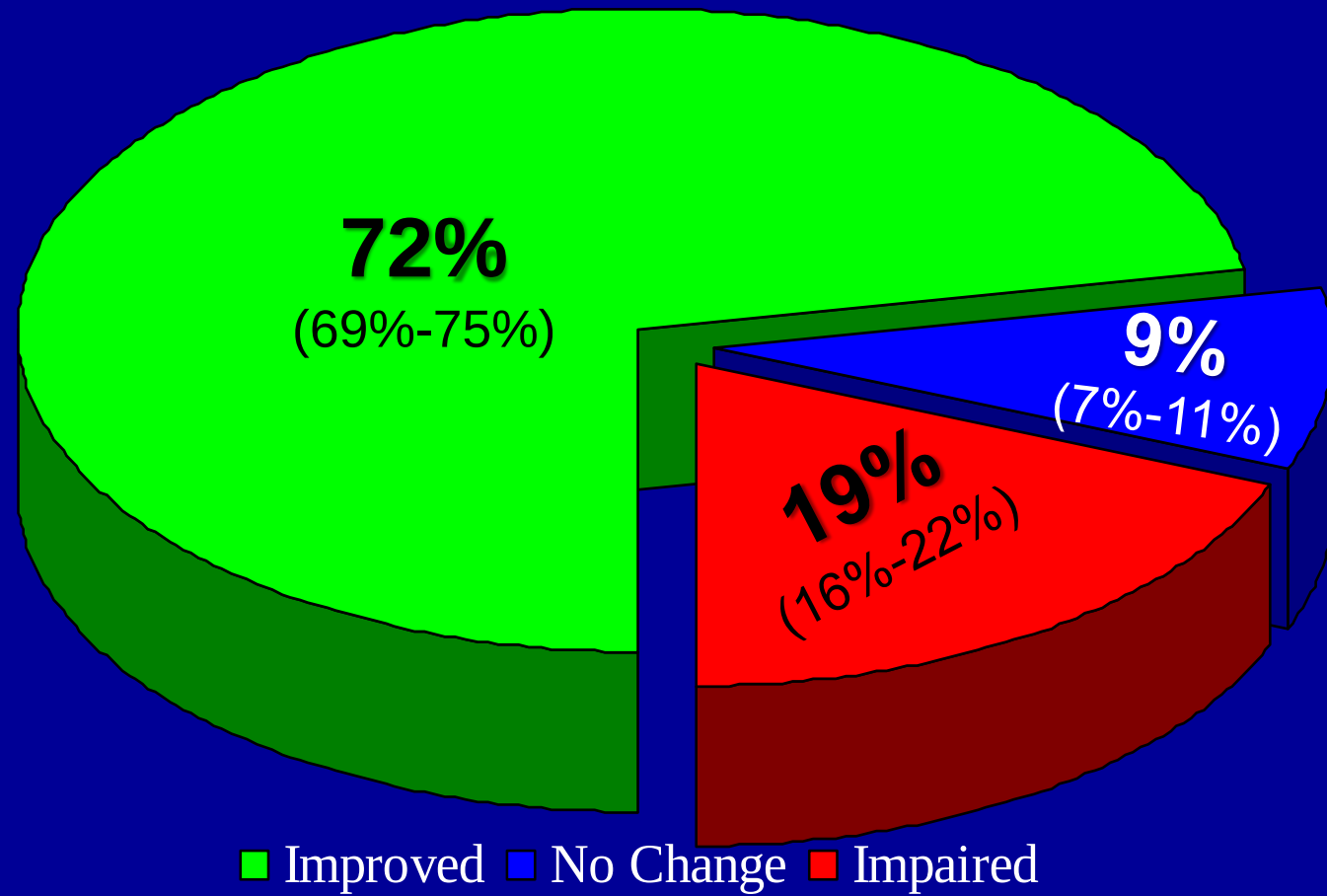
Retinal Vasculitis – % Improvement



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

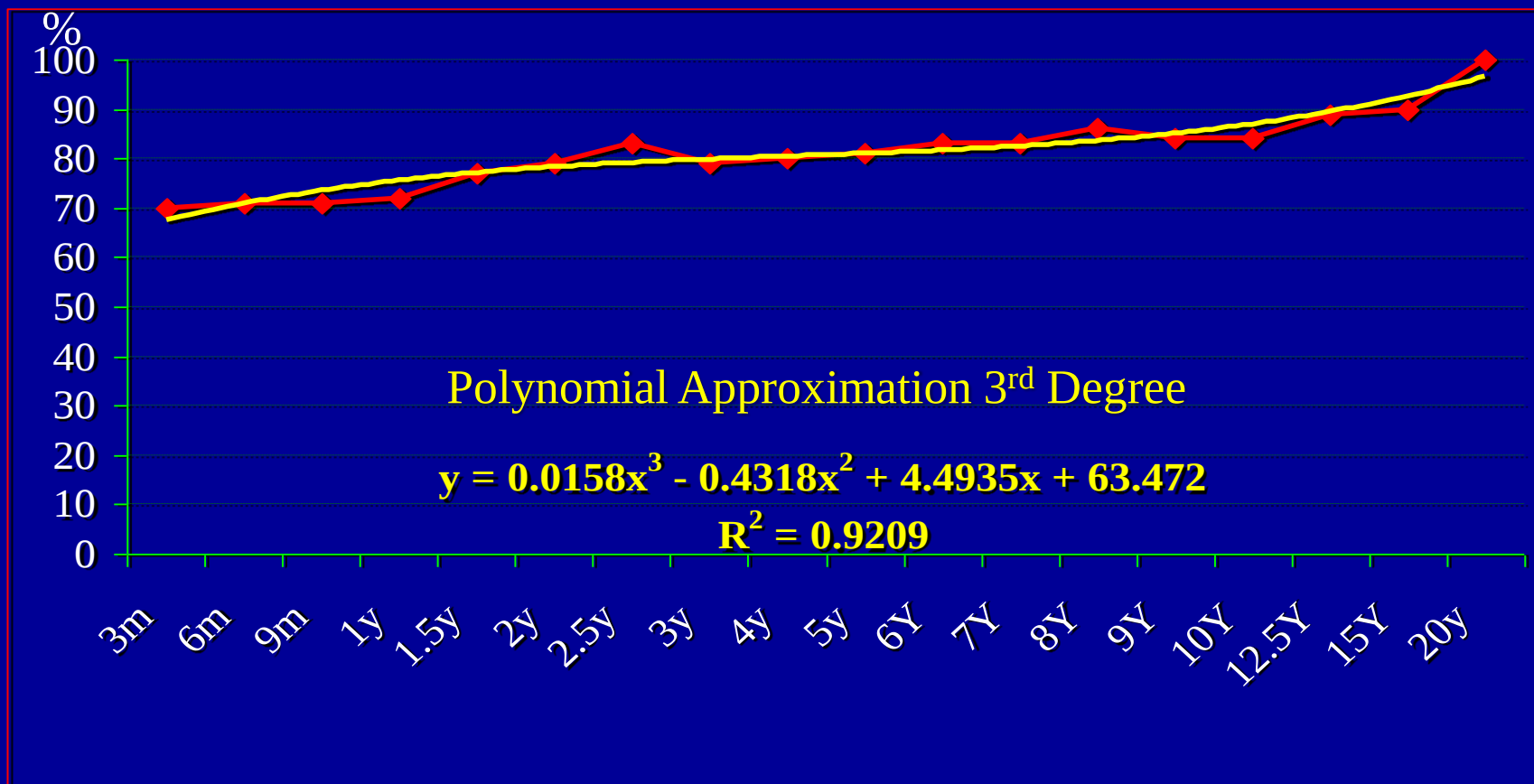
$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$

MTX



Longitudinal Study

T_{total} A_{adjusted} D_{disease} A_{activity} I_{index} — % Improvement



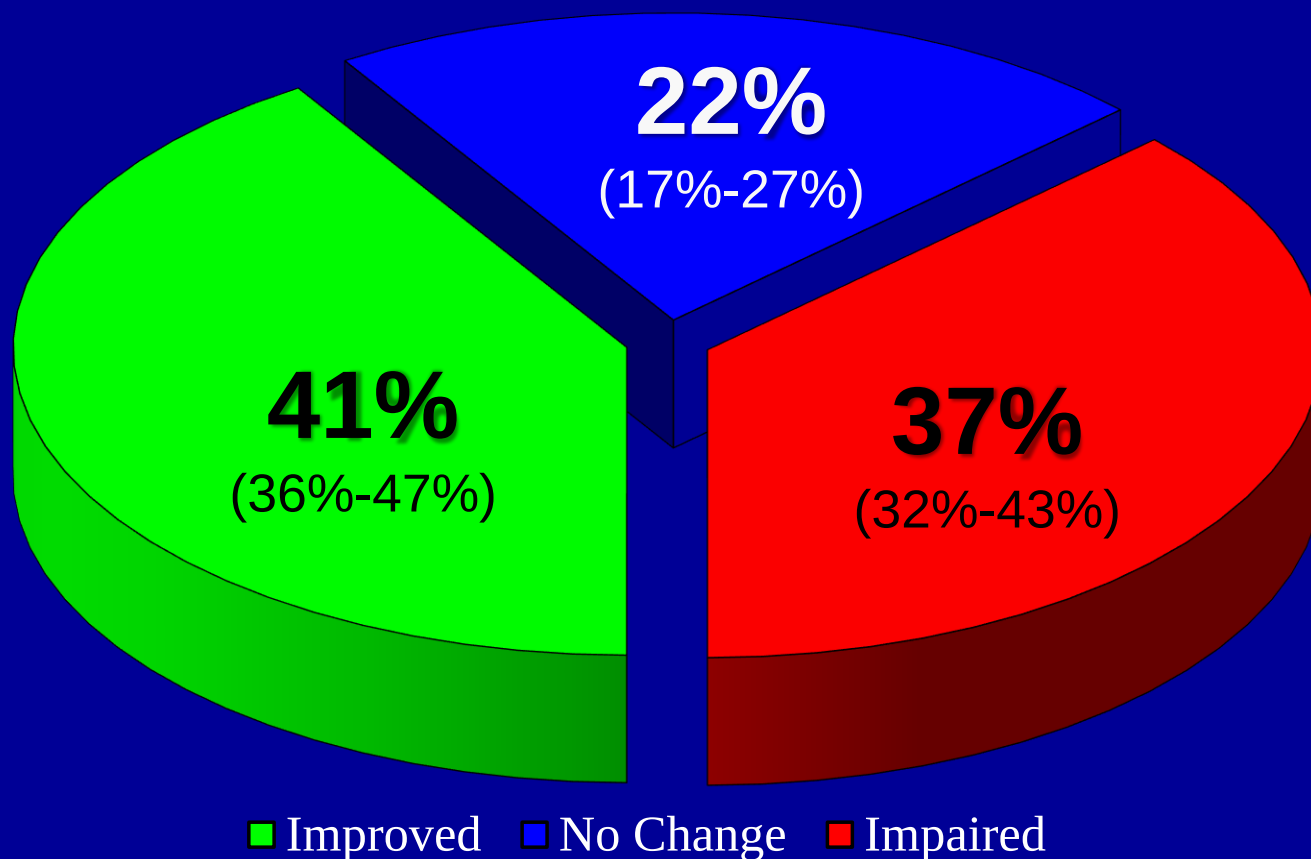
AZATHIOPRINE

204 Patients

Longitudinal Study up to 15 Years

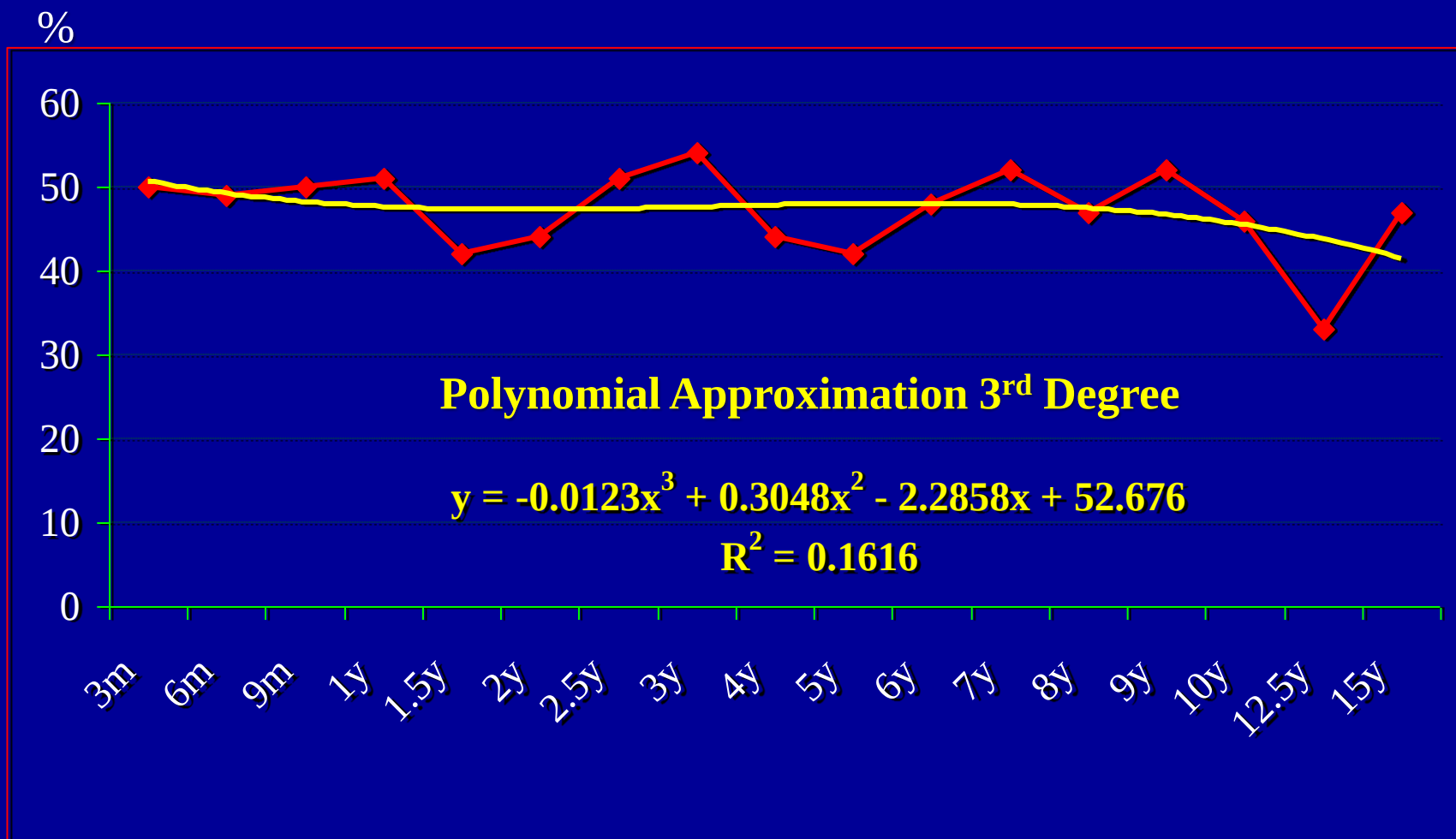
VISUAL ACUITY

AZA



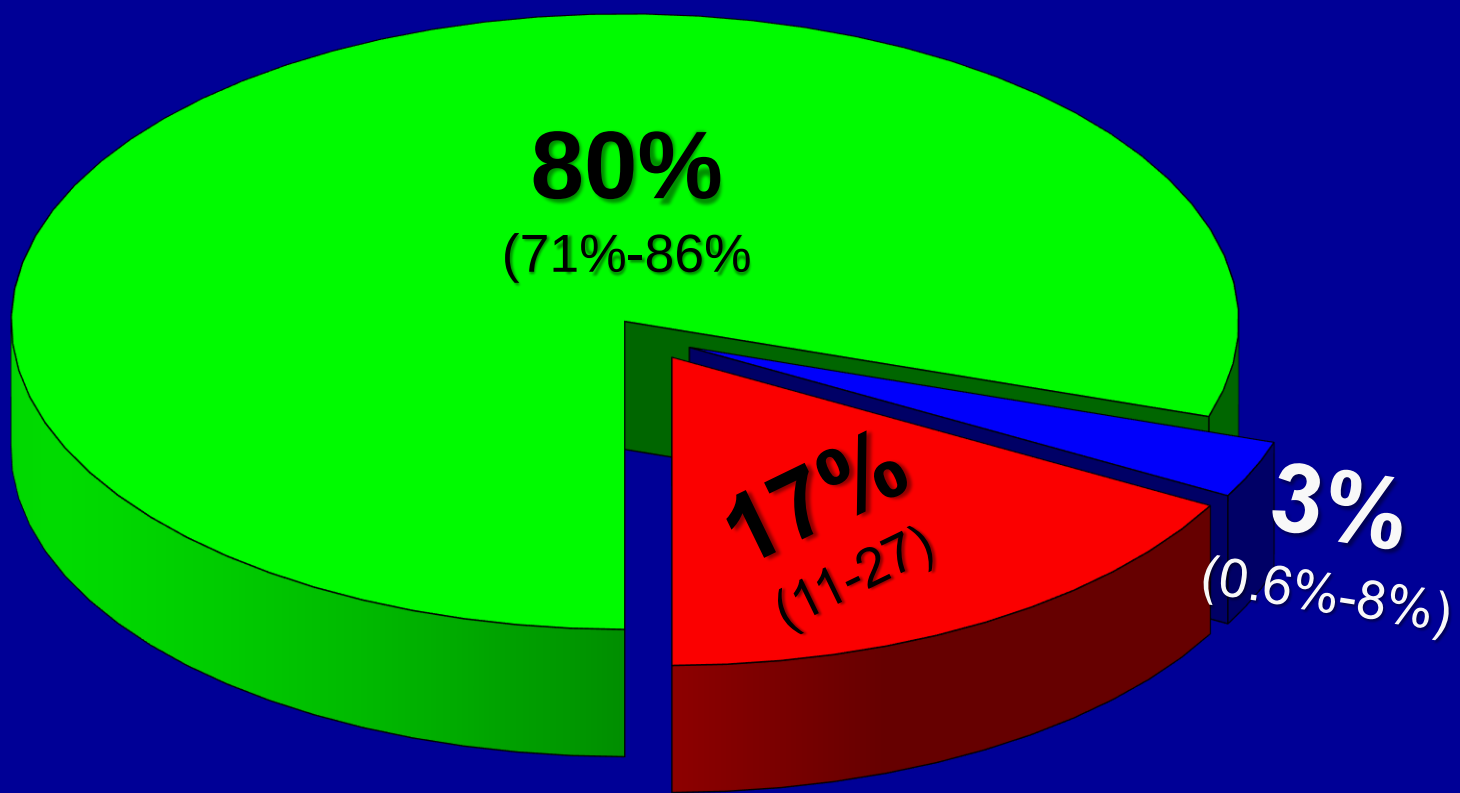
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

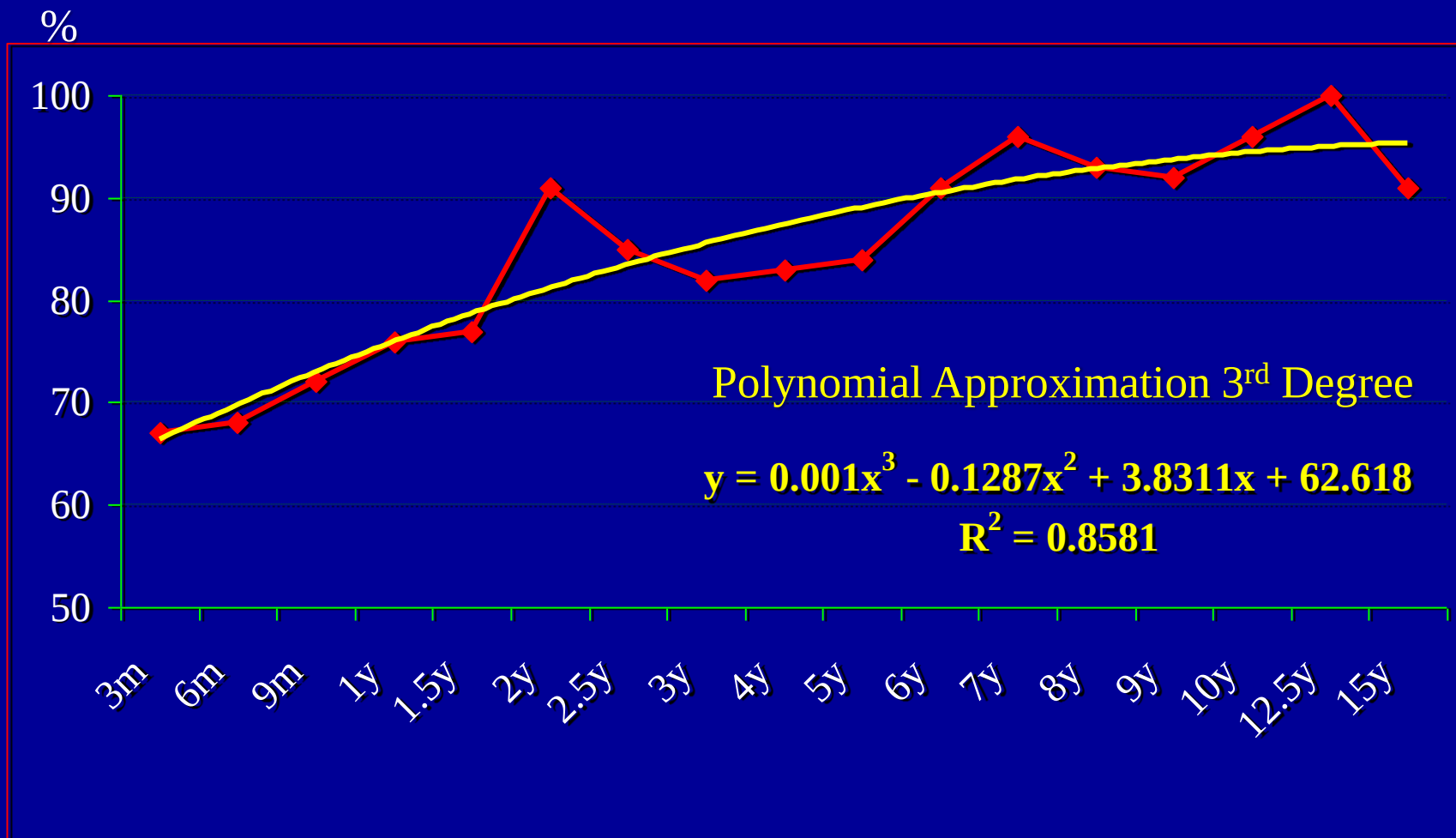
AZA



■ Improved ■ No Change ■ Impaired

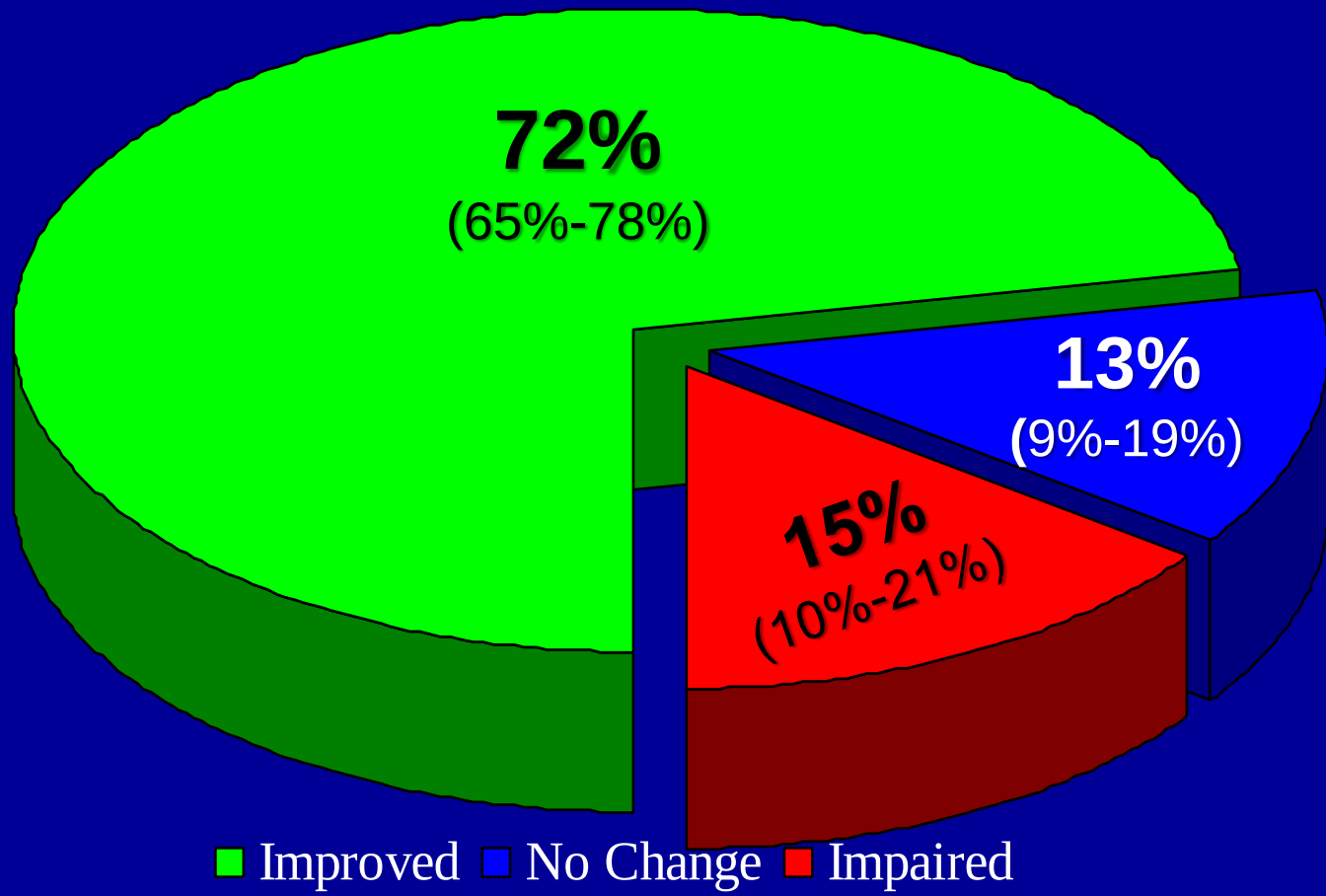
Longitudinal Study

Anterior Uveitis – % Improvement



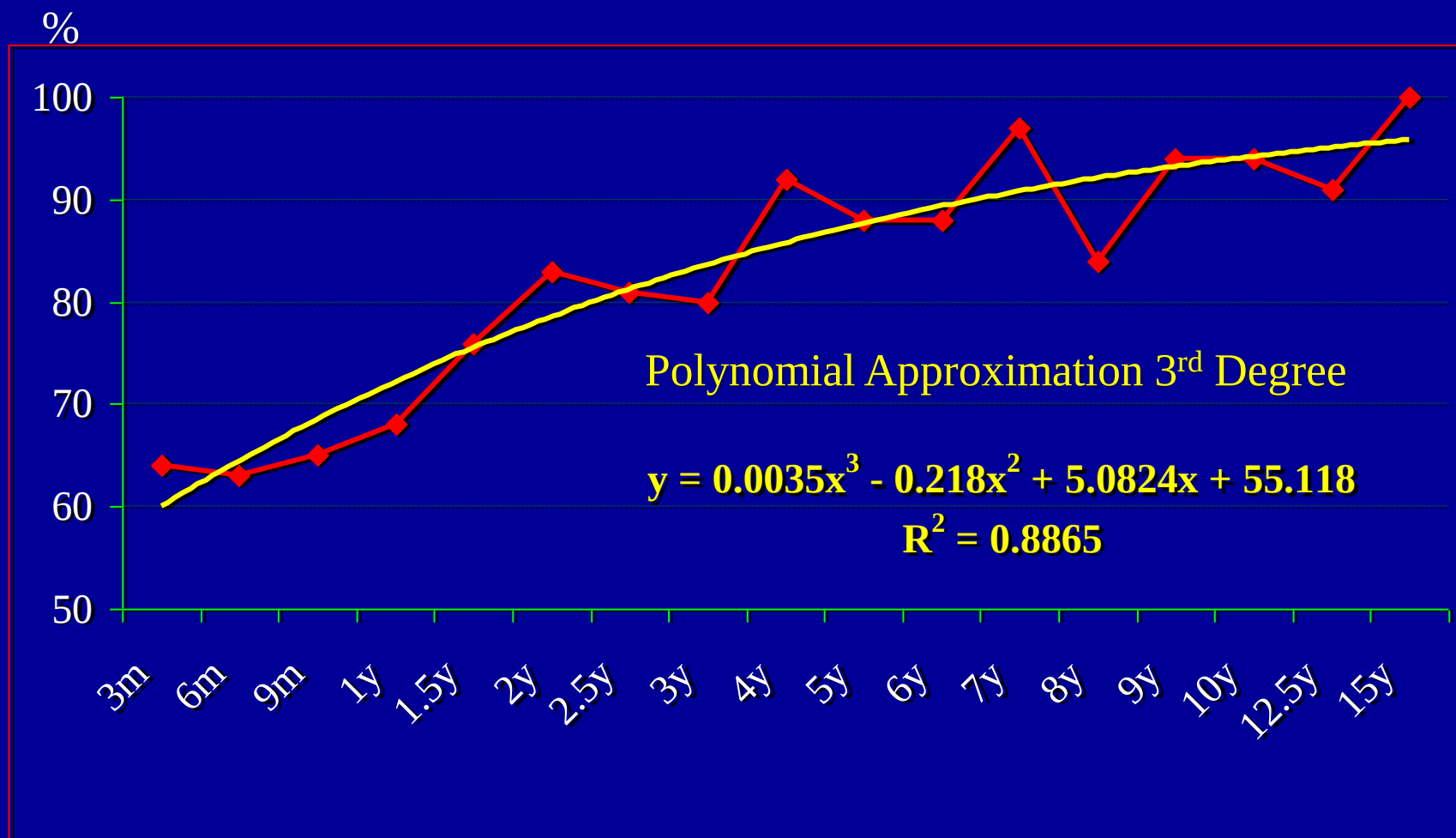
POSTERIOR UVEITIS

AZA



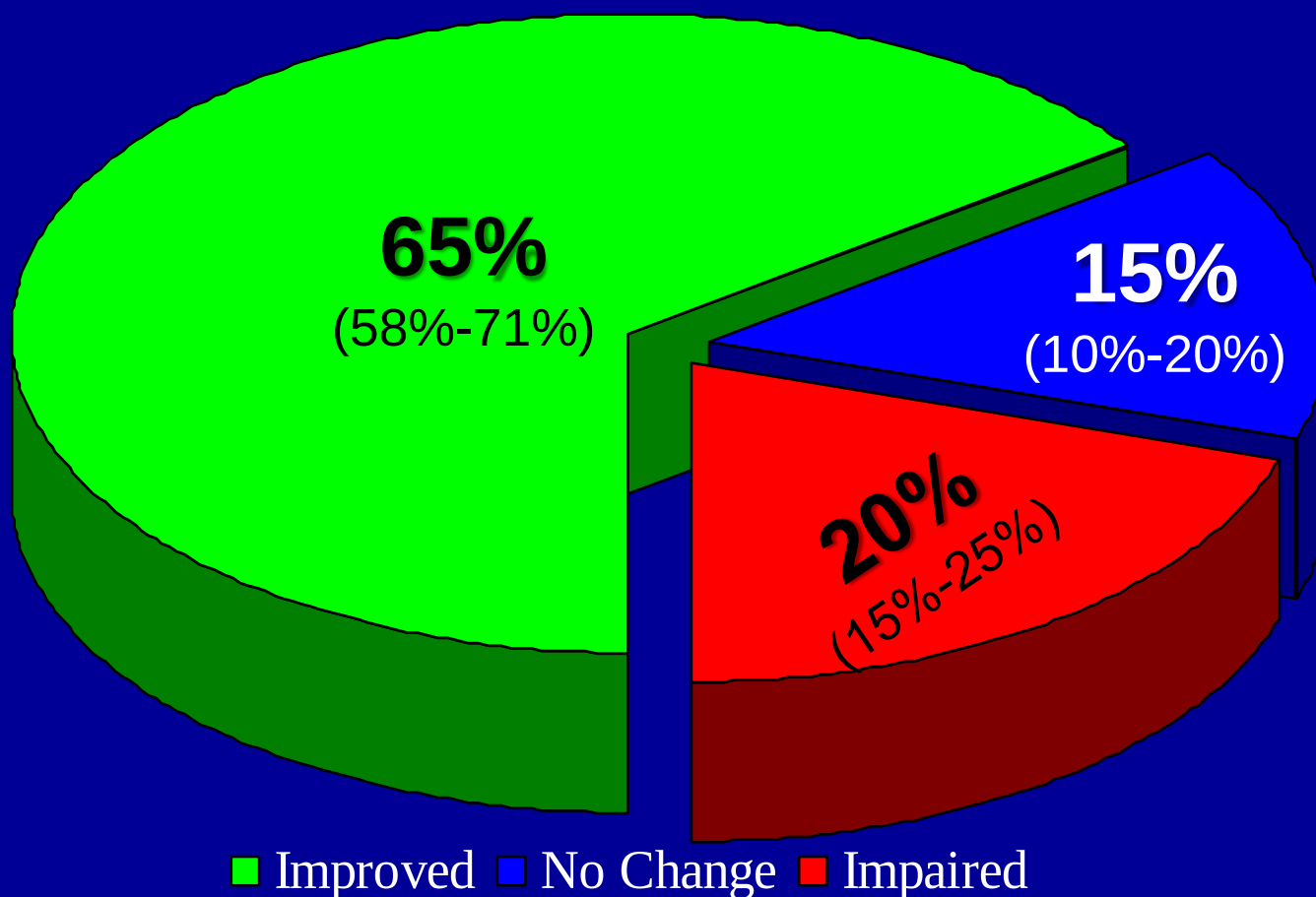
Longitudinal Study

Posterior Uveitis – % Improvement



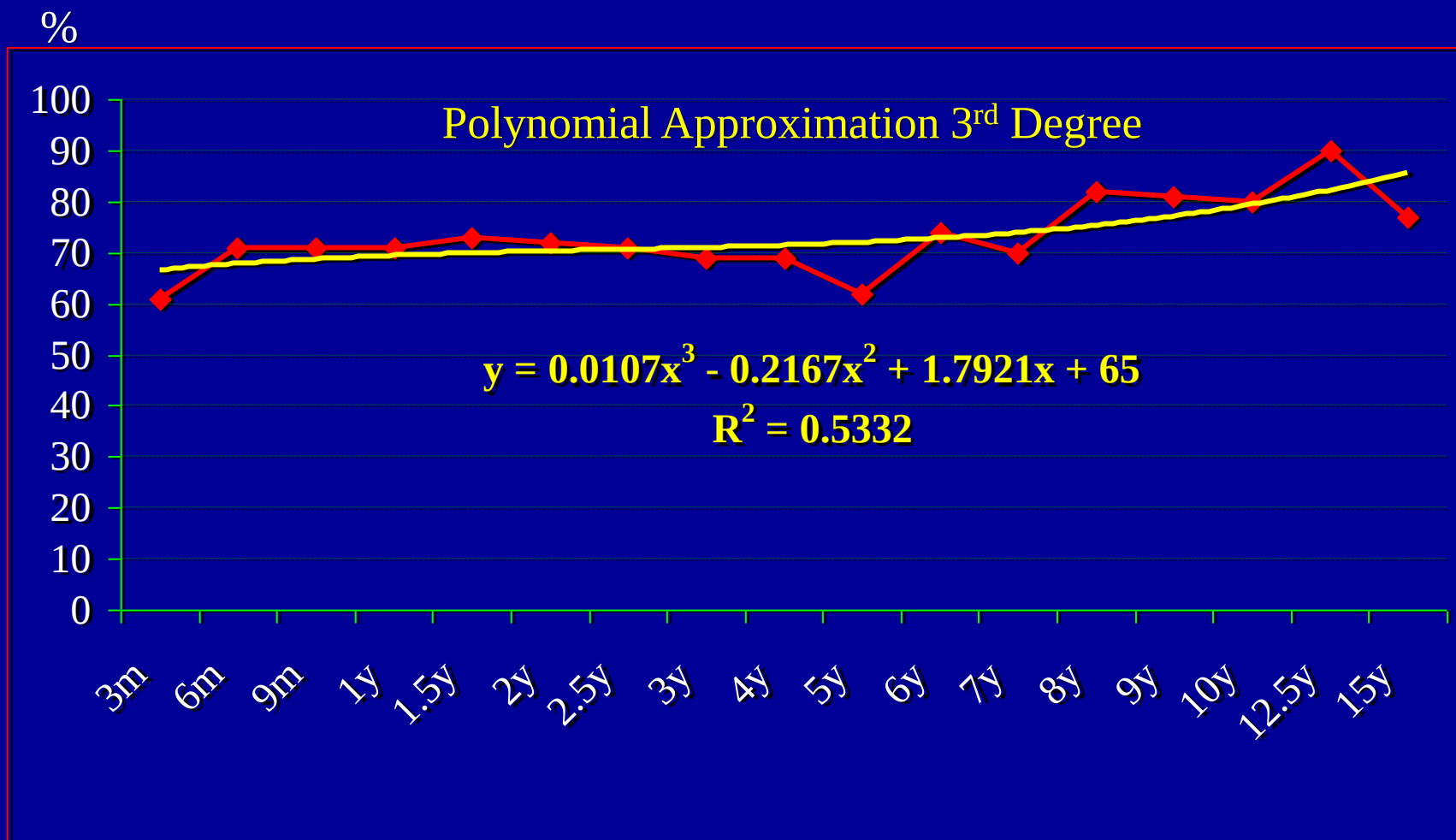
RETINAL VASCULITIS

AZA



Longitudinal Study

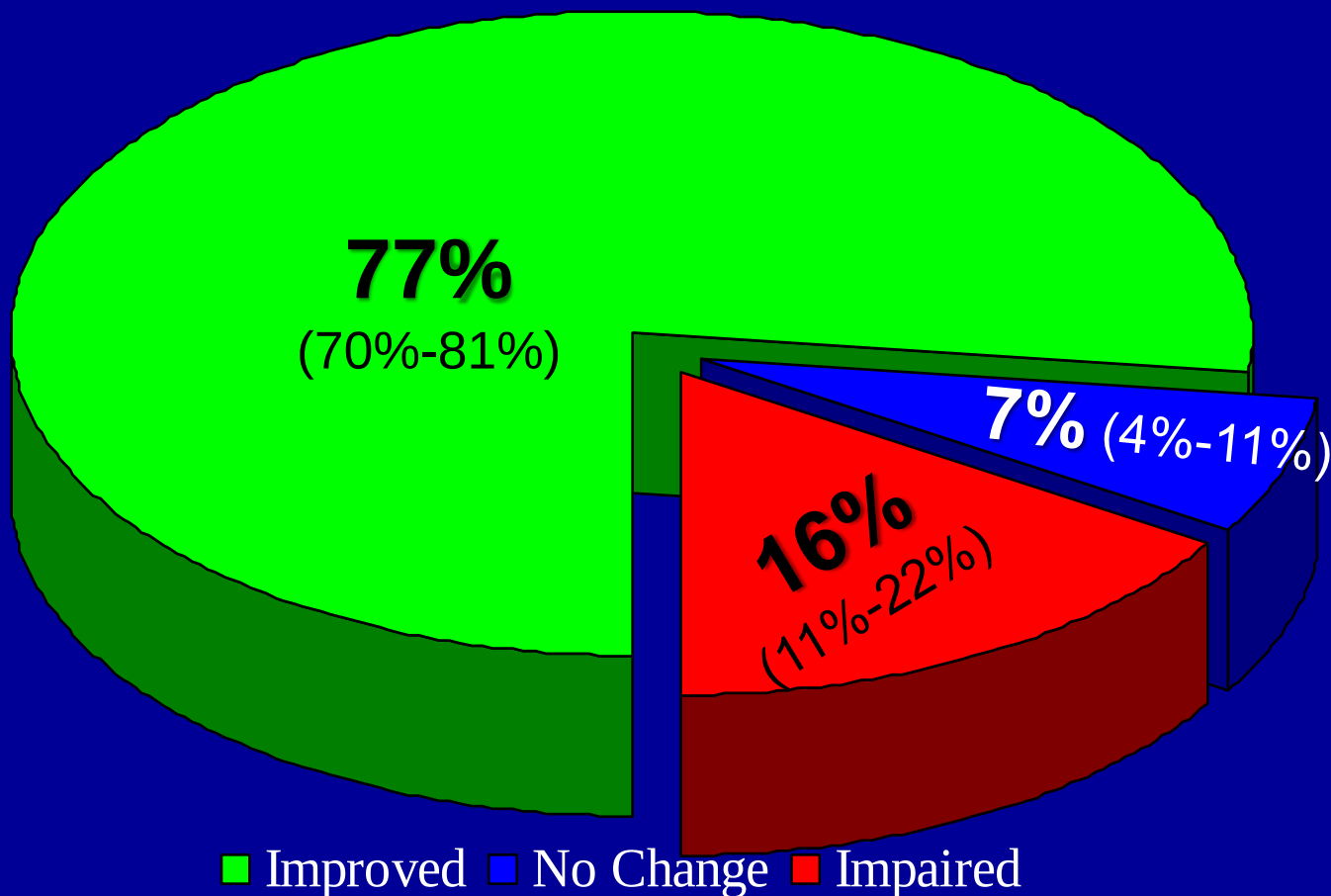
Retinal Vasculitis – % Improvement



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

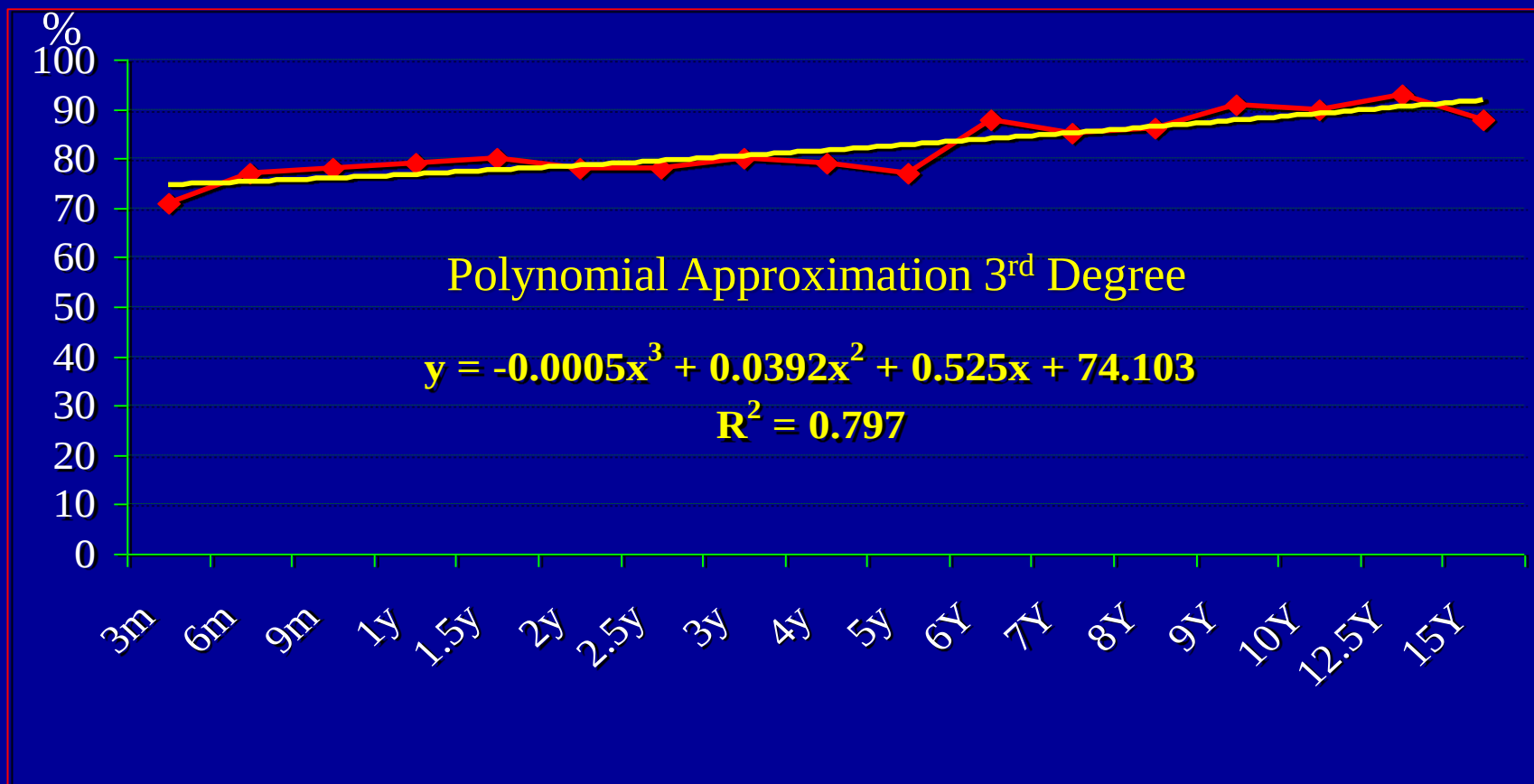
$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$

AZA



Longitudinal Study

T_{total} A_{adjusted} D_{disease} A_{activity} I_{index} — % Improvement



یازدهمین کنگره سالیانه انجمن روماتولوژی ایران

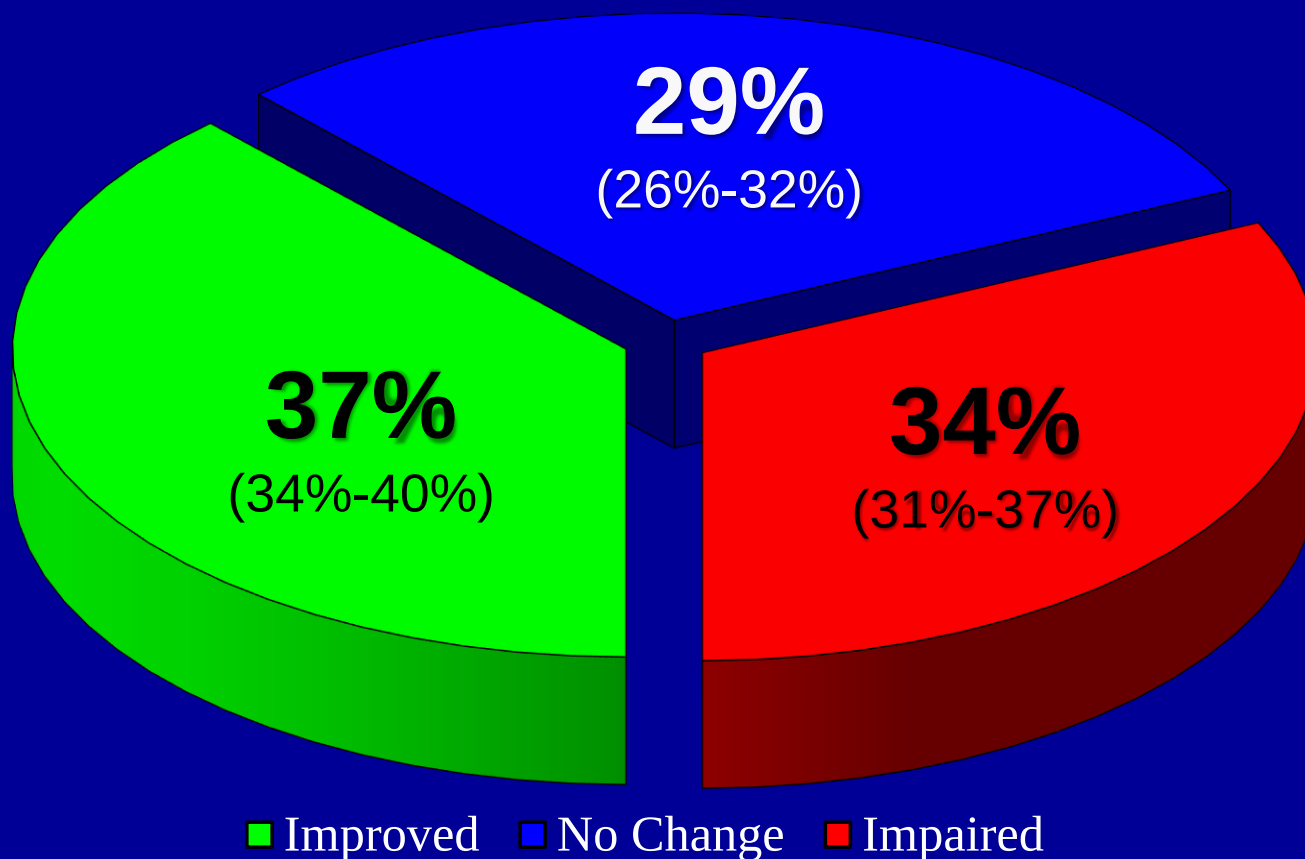
PULSE CYCLOPHOSPHAMIDE

538 Patients

Longitudinal Study up to 20 Years

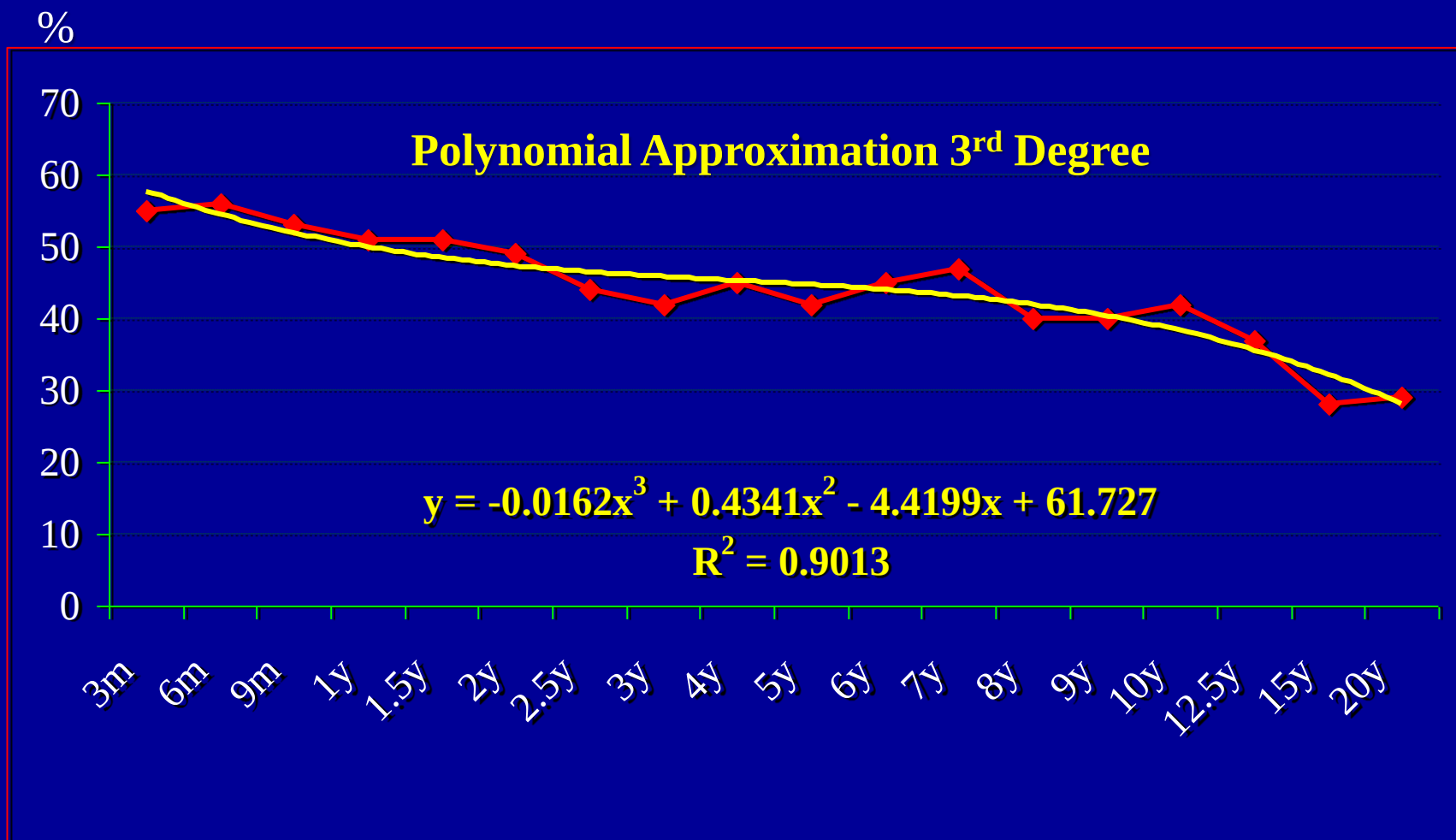
VISUAL ACUITY

PCP



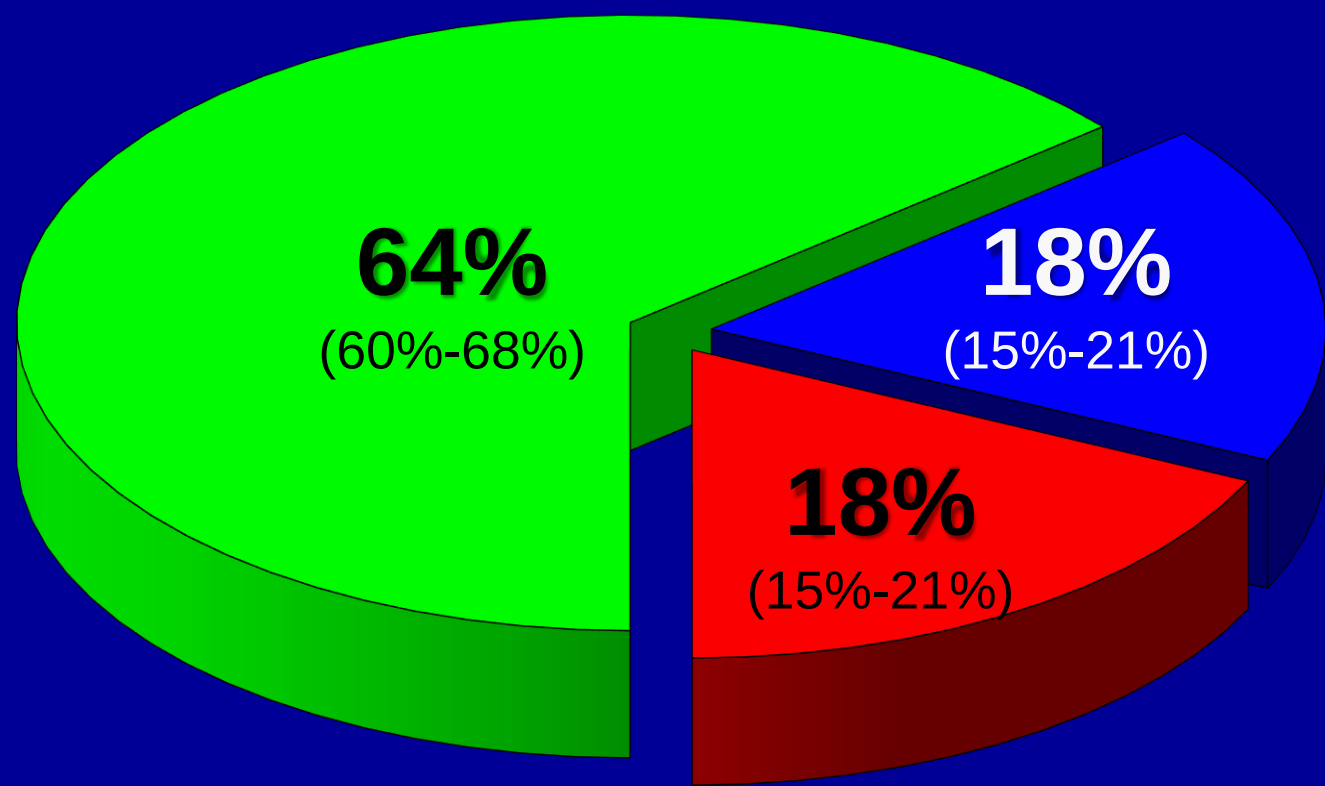
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

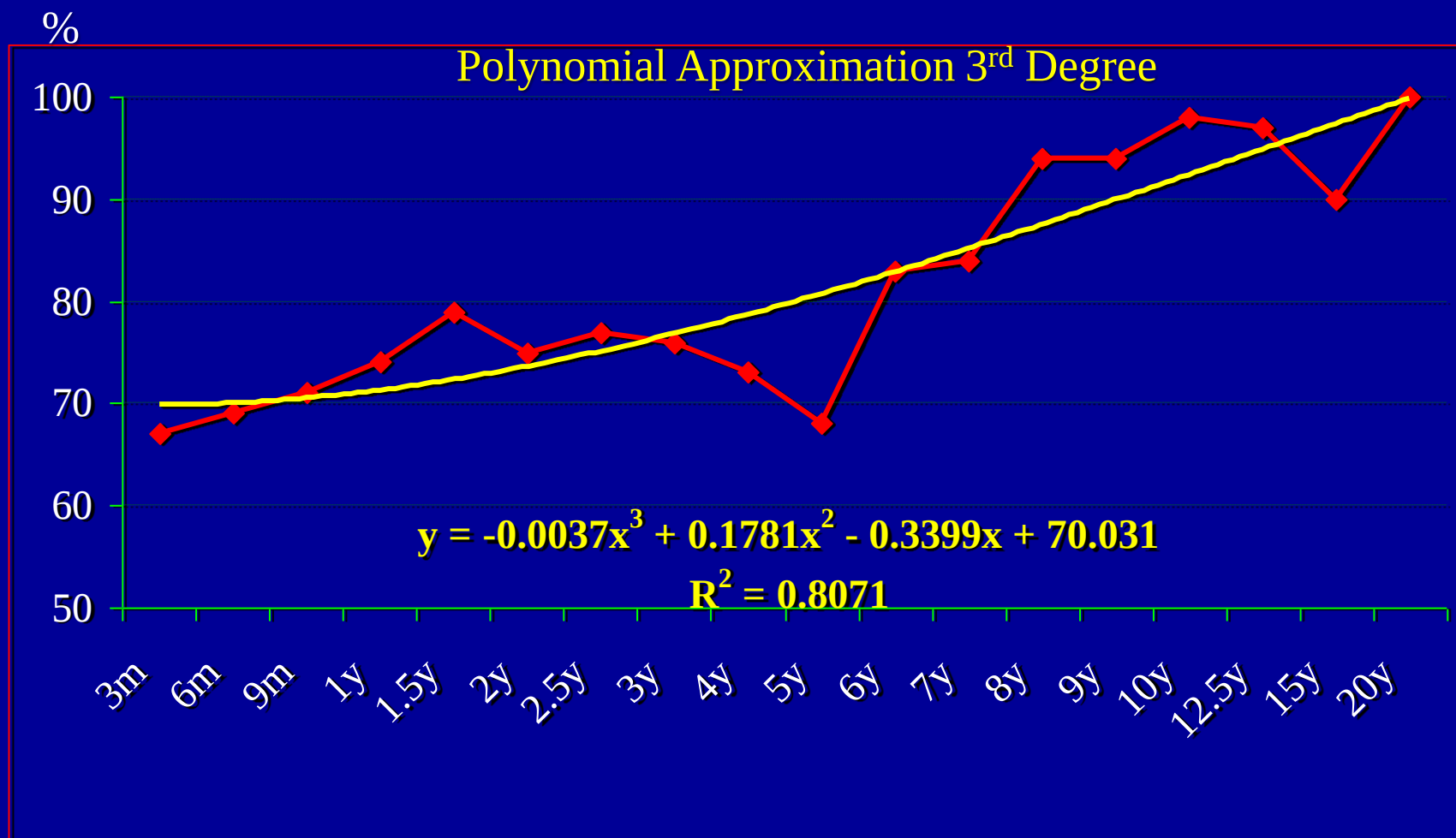
PCP



■ Improved ■ No Change ■ Impaired

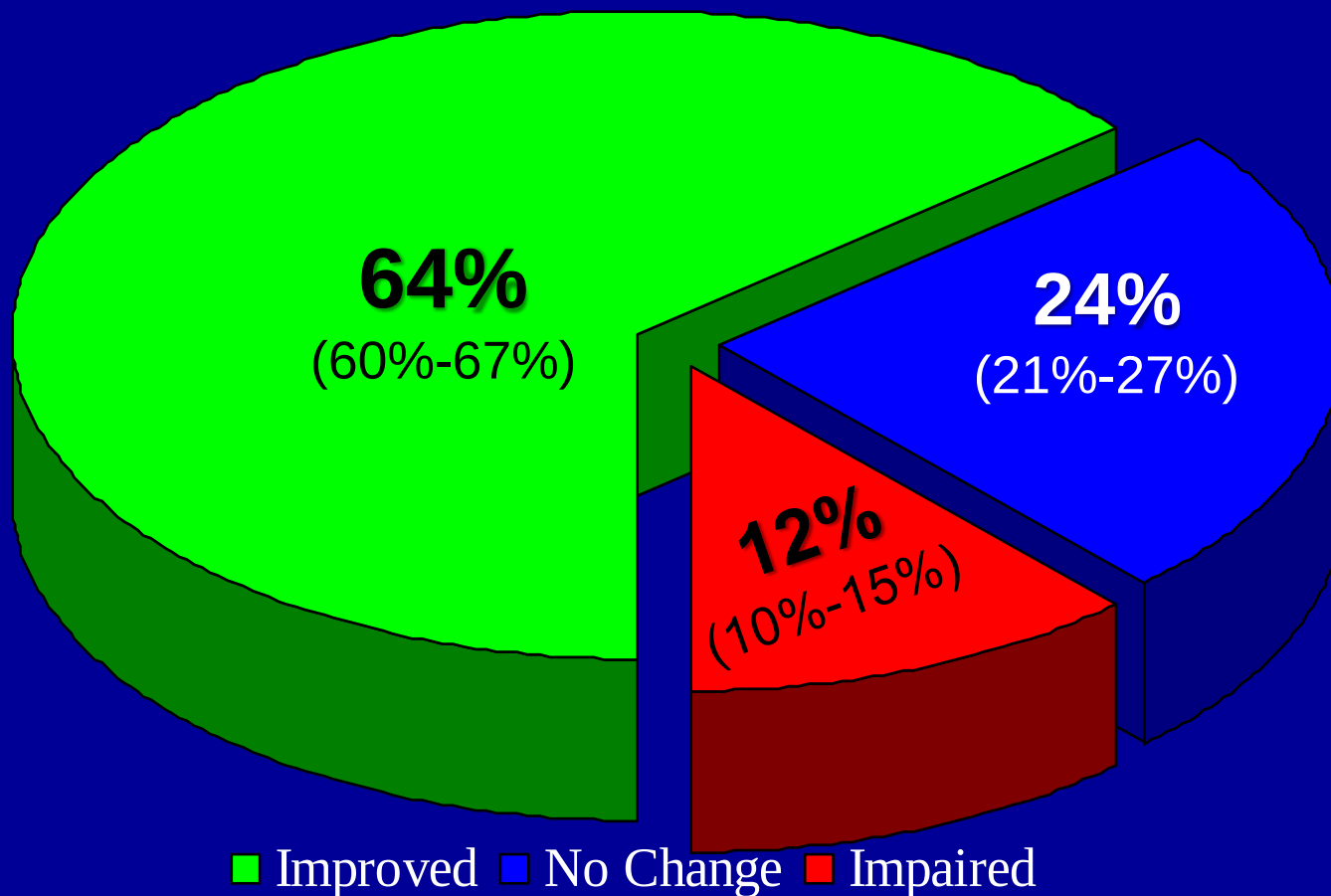
Longitudinal Study

Anterior Uveitis – % Improvement



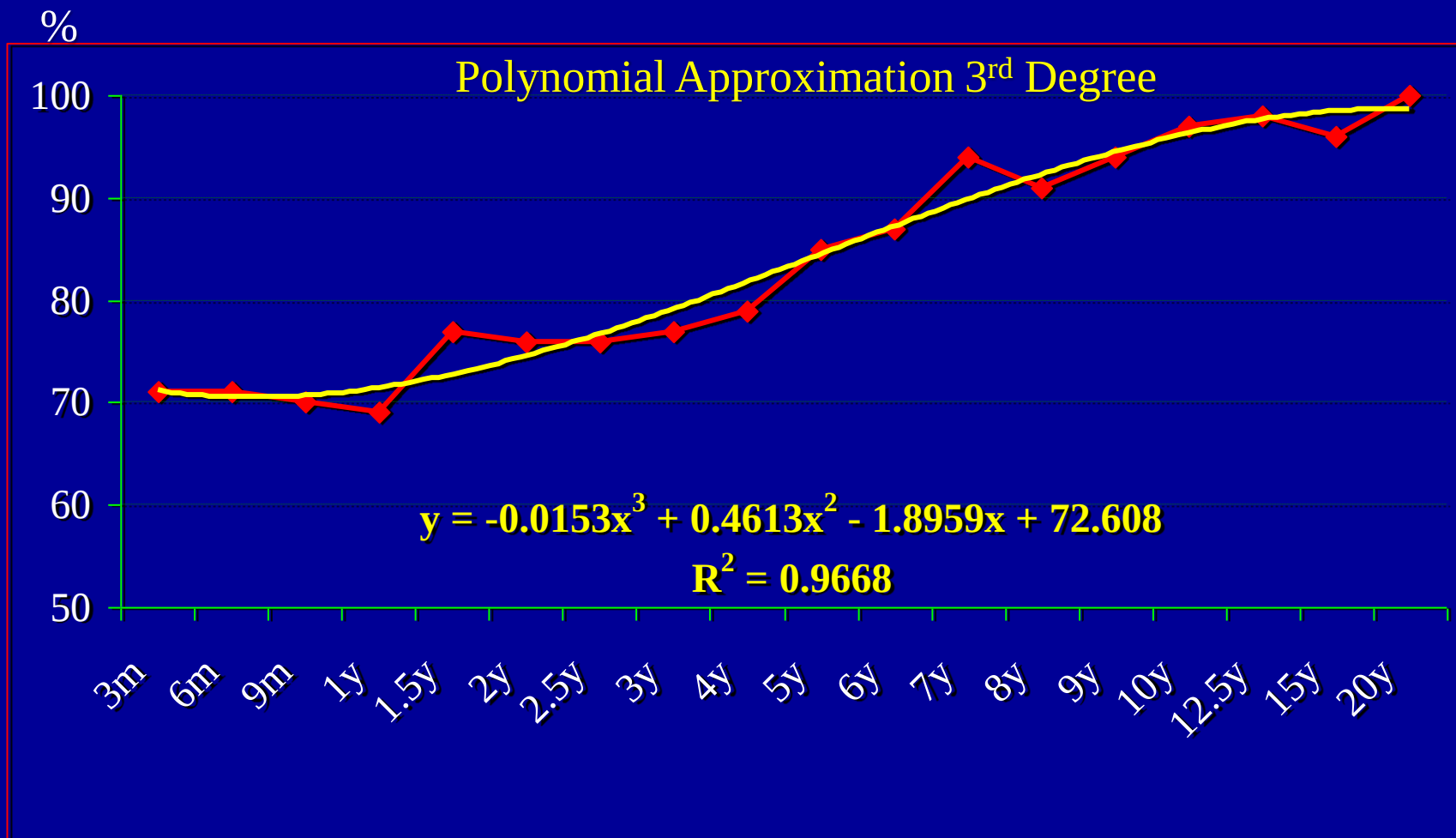
POSTERIOR UVEITIS

PCP



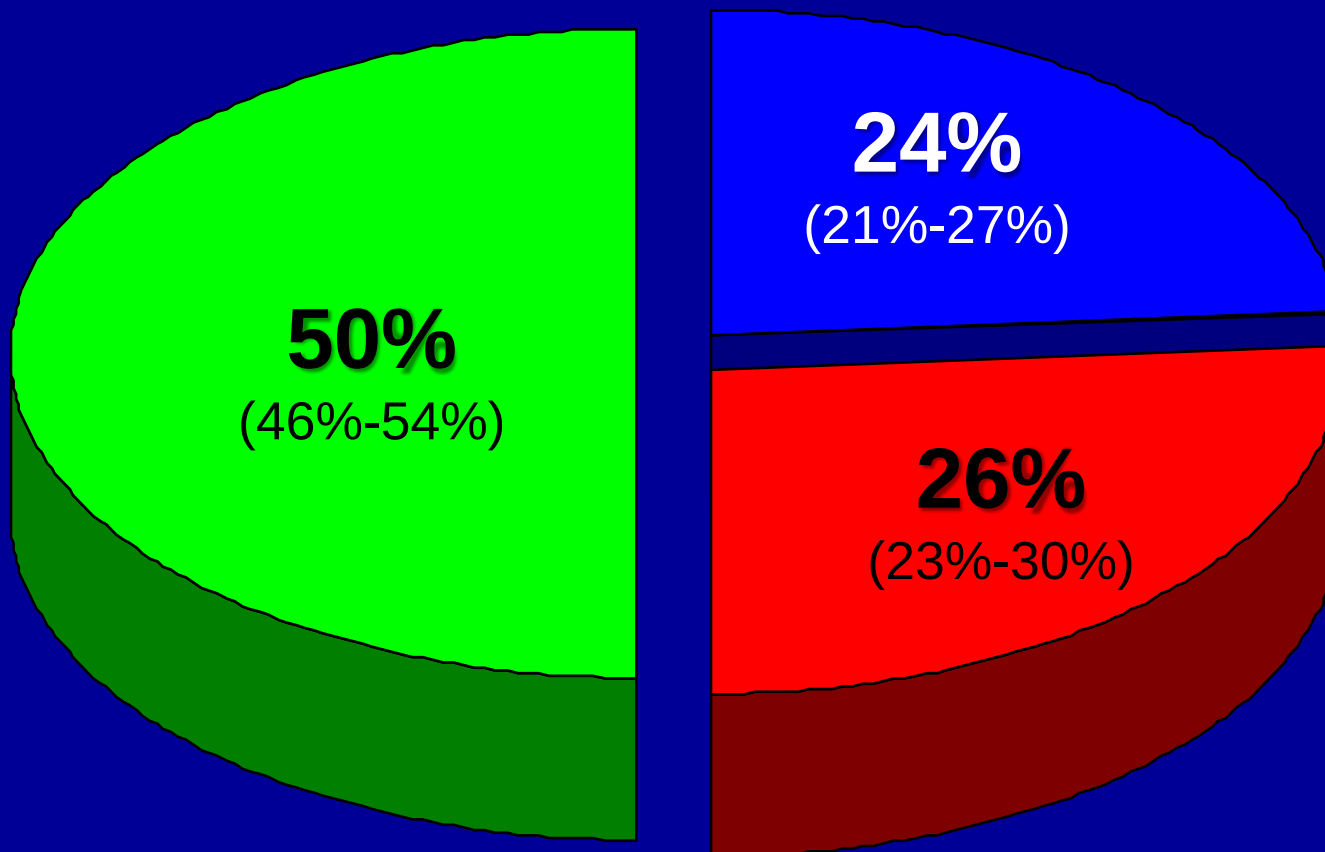
Longitudinal Study

Posterior Uveitis – % Improvement



RETINAL VASCULITIS

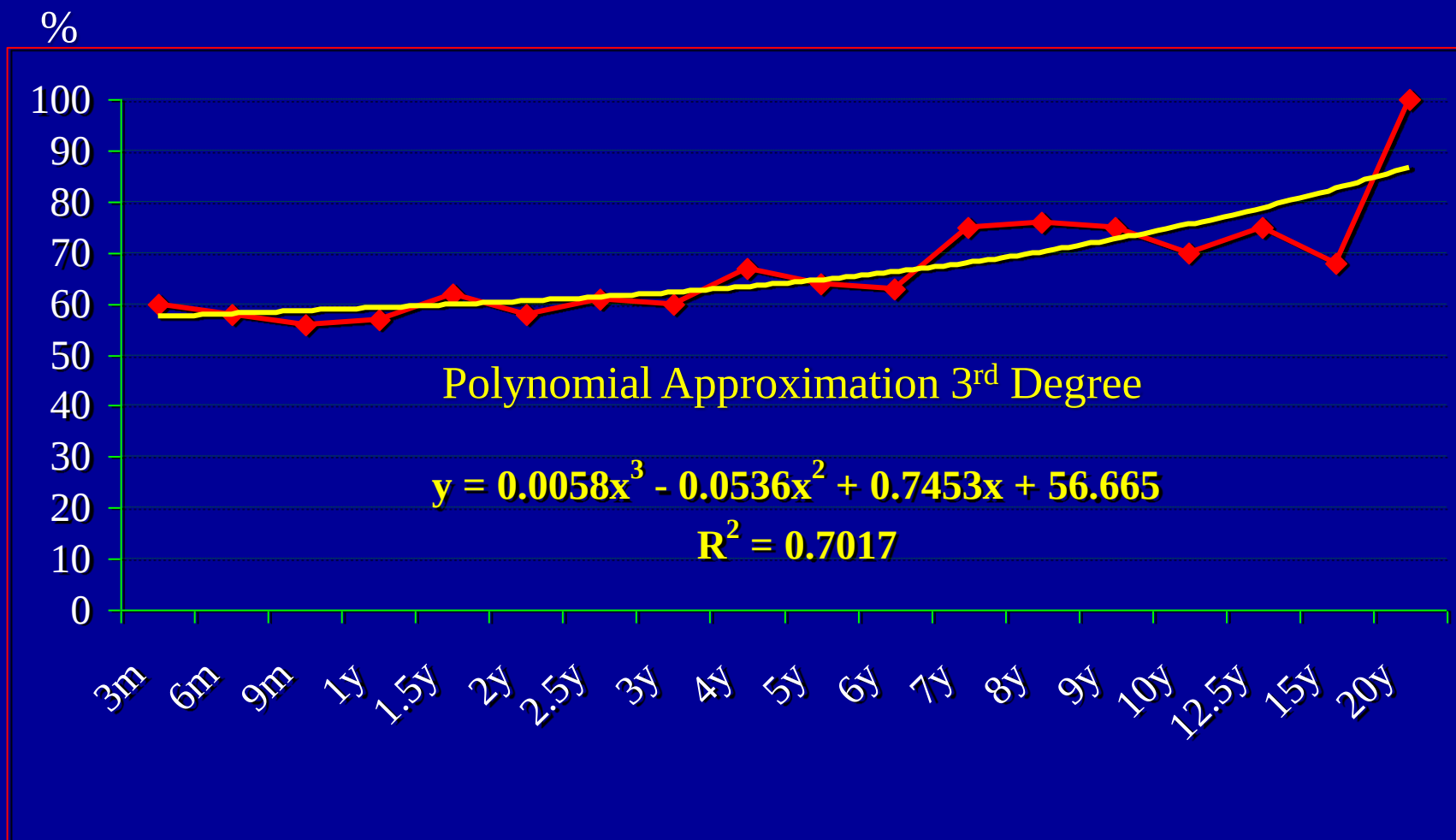
PCP



■ Improved ■ No Change ■ Impaired

Longitudinal Study

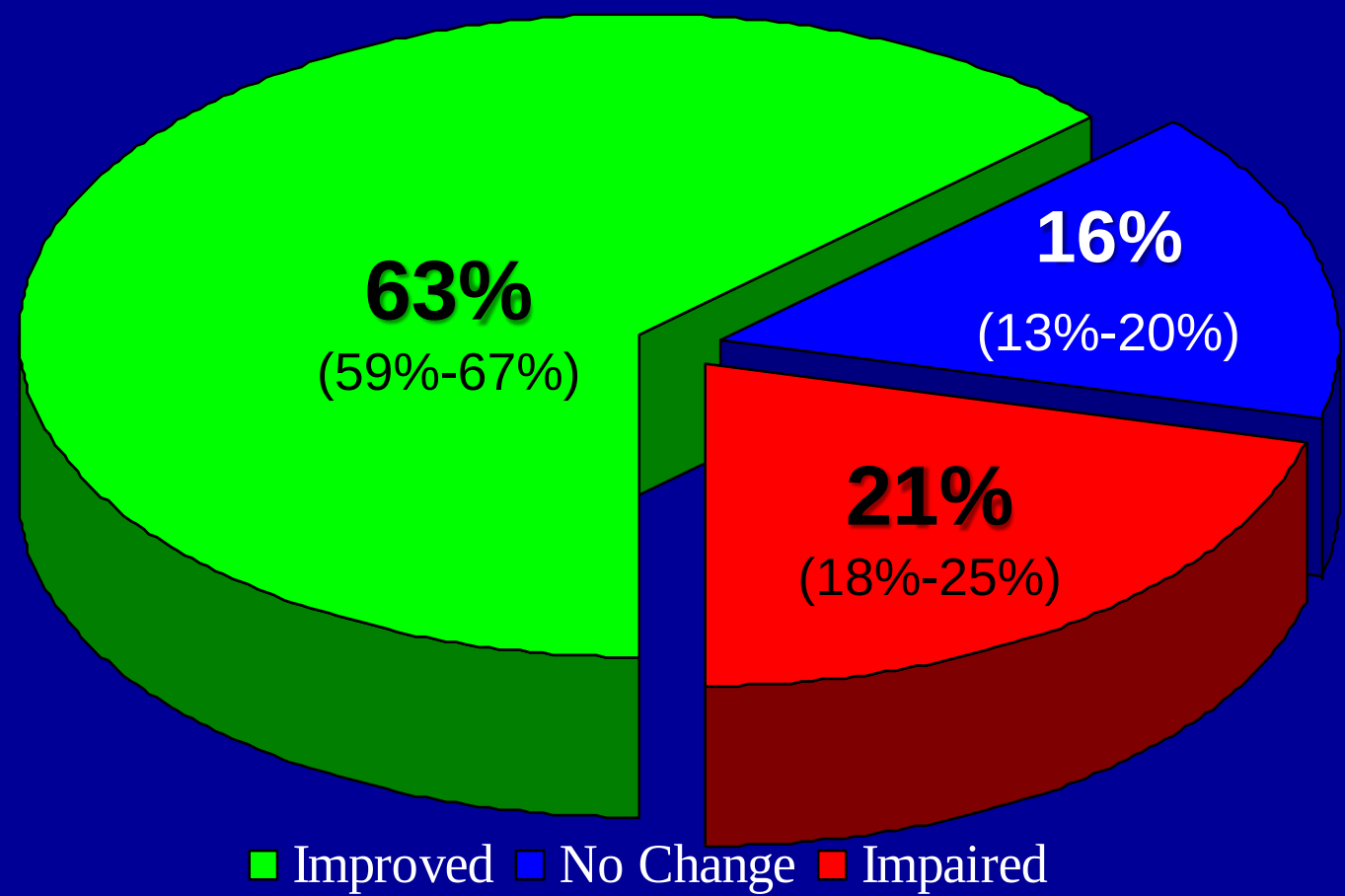
Retinal Vasculitis – % Improvement



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

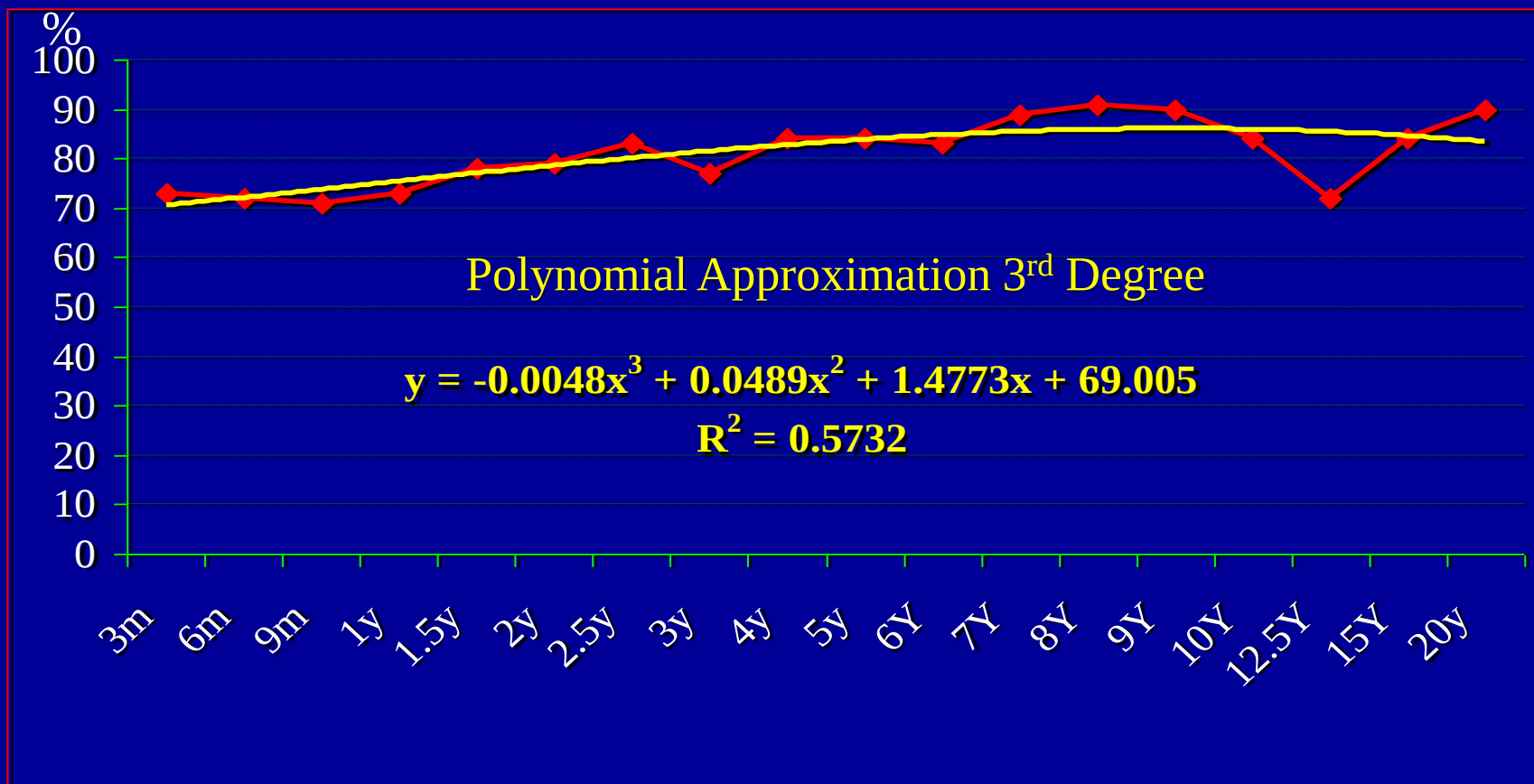
$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$

PCP



Longitudinal Study

T_{total} A_{adjusted} D_{disease} A_{activity} I_{index} — % Improvement



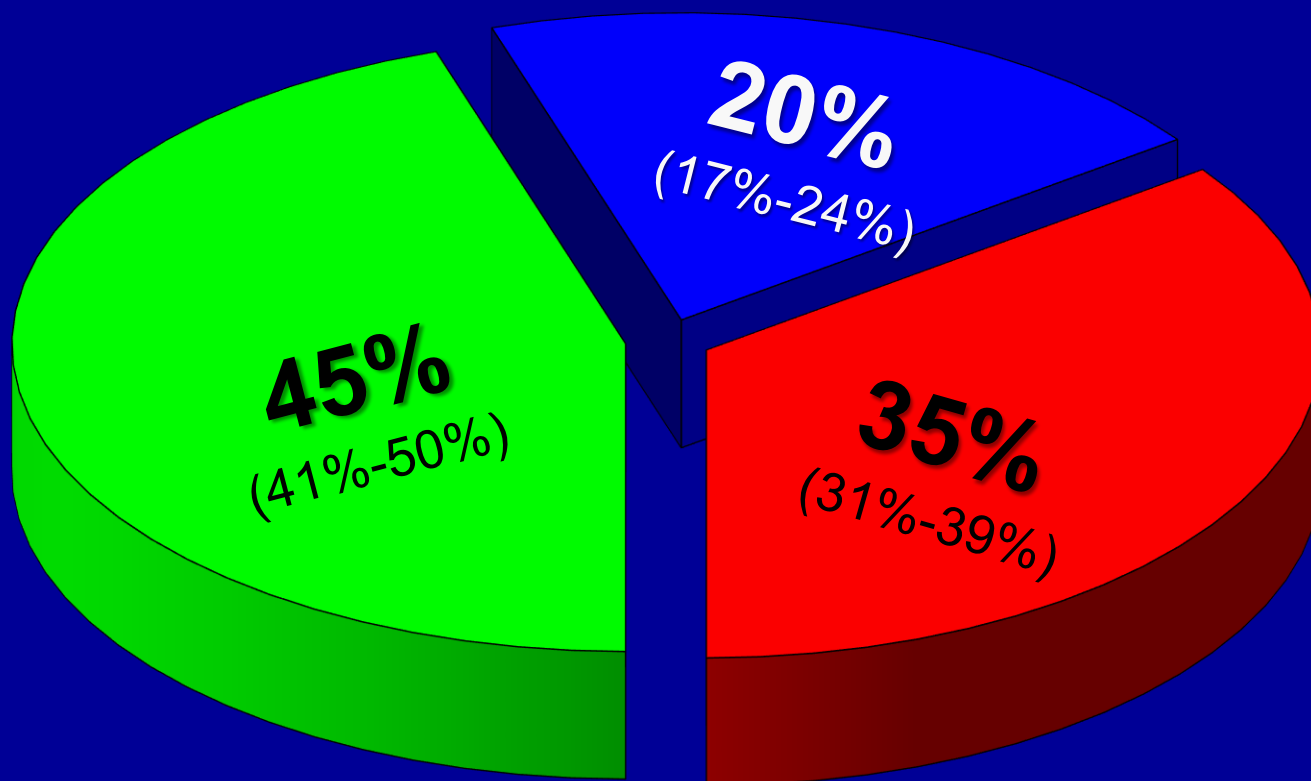
PULSE CYCLOPHOSPHAMIDE & AZATHIOPRINE

389 Patients

Longitudinal Study up to 15 Years

VISUAL ACUITY

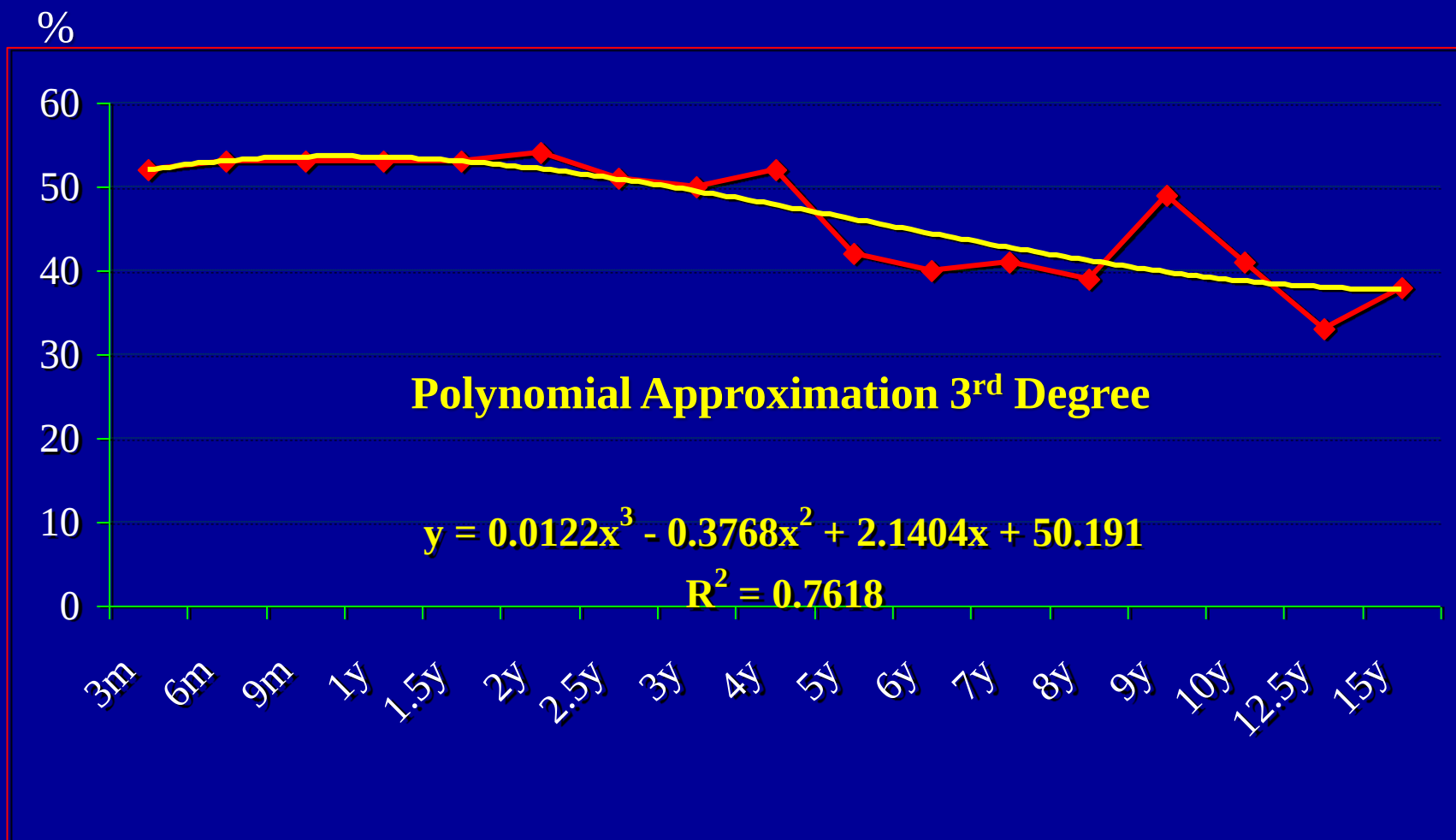
PCP + AZA



■ Improved ■ No Change ■ Impaired

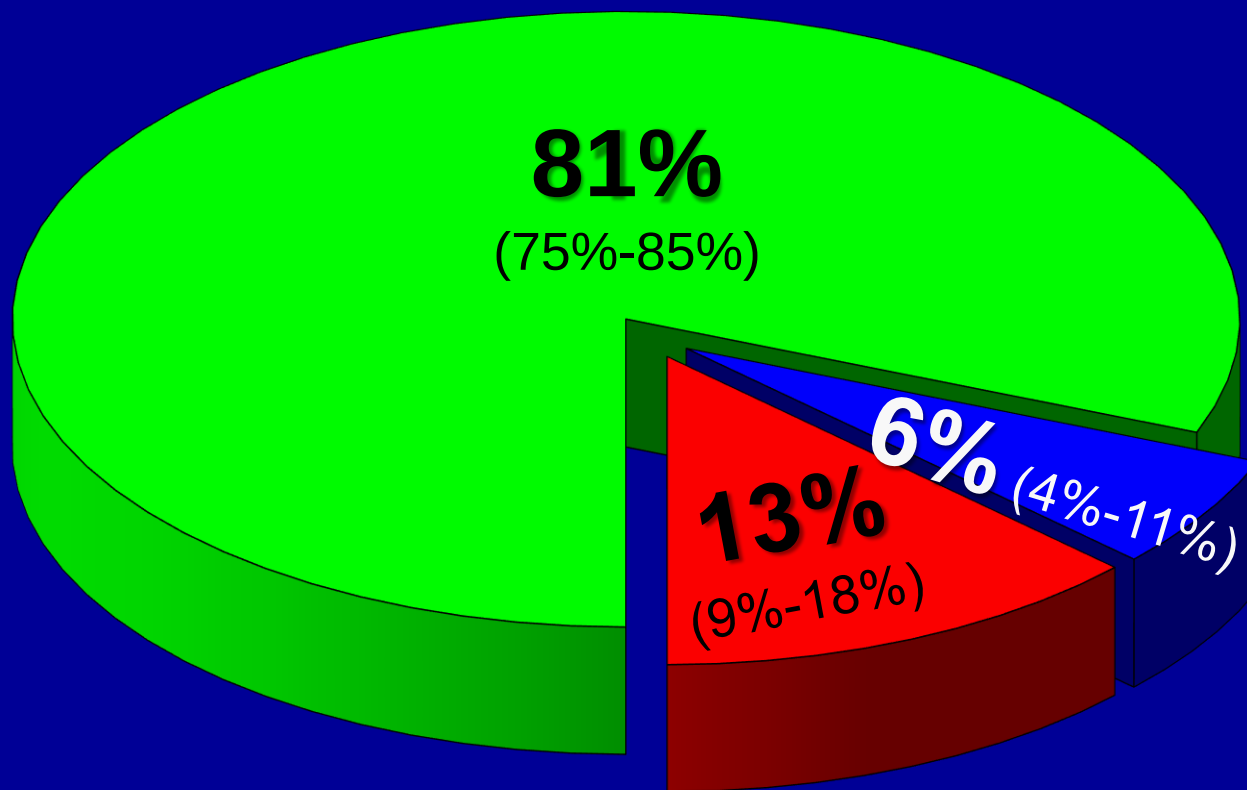
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

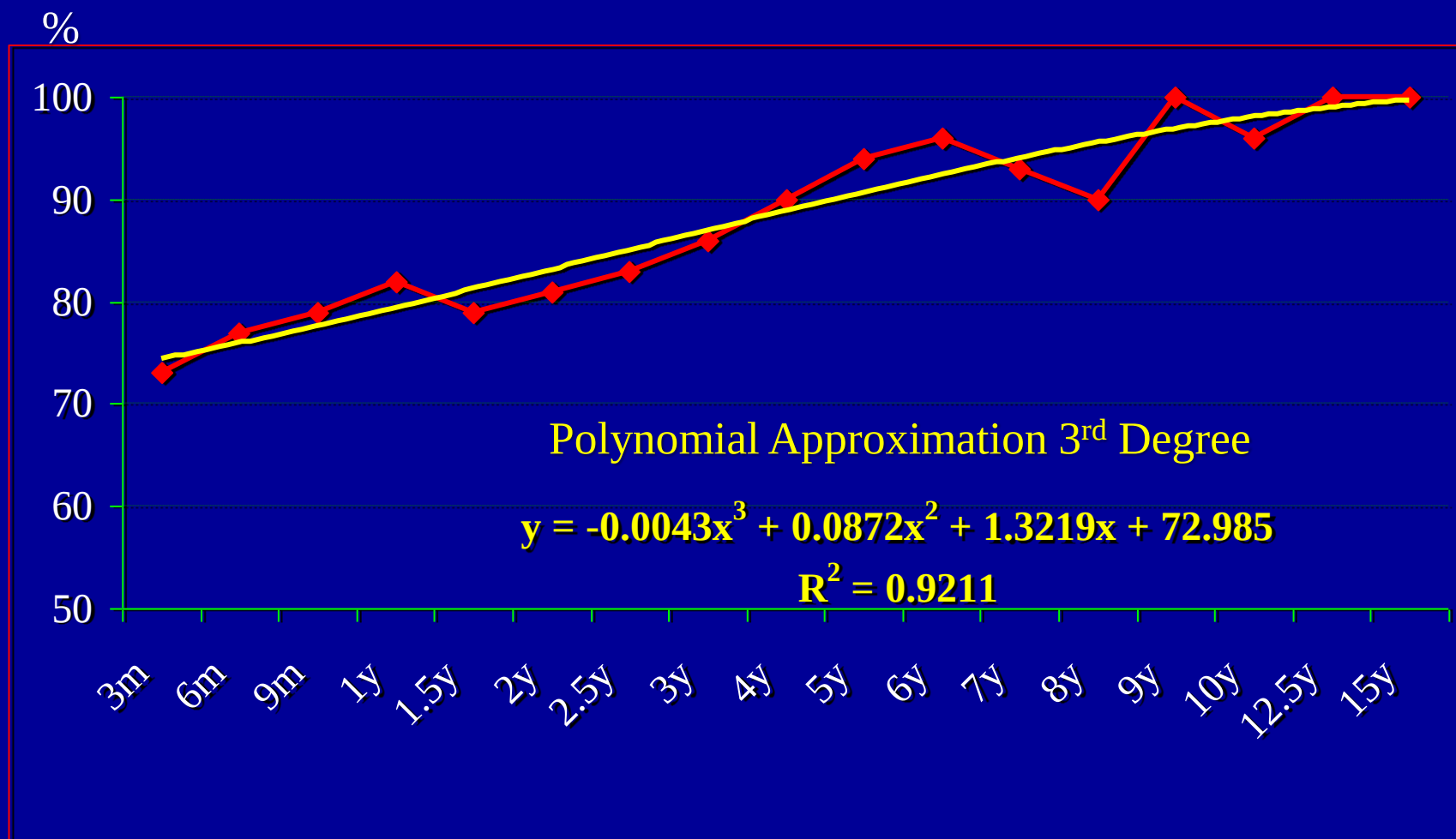
PCP + AZA



■ Improved ■ No Change ■ Impaired

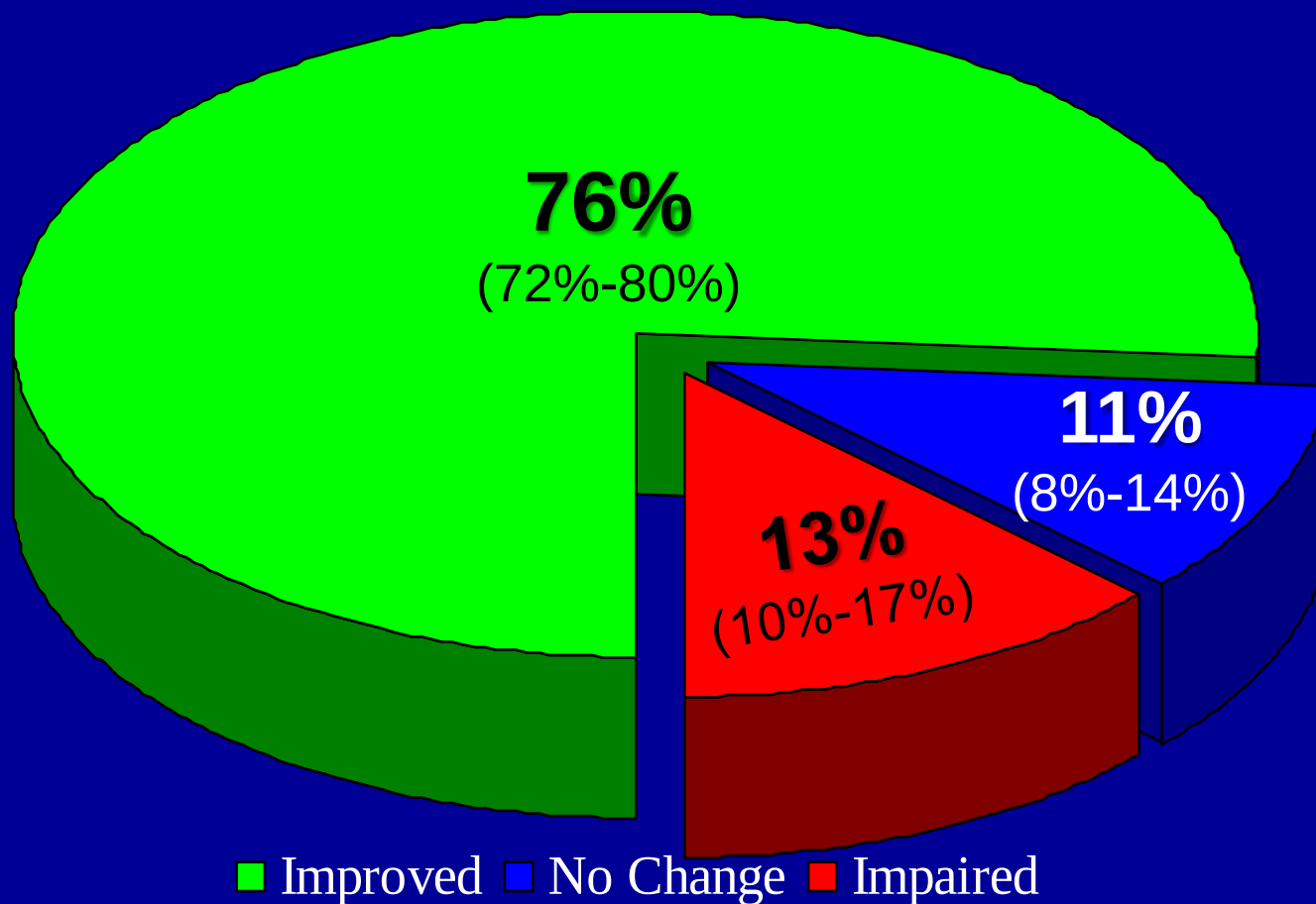
Longitudinal Study

Anterior Uveitis – % Improvement



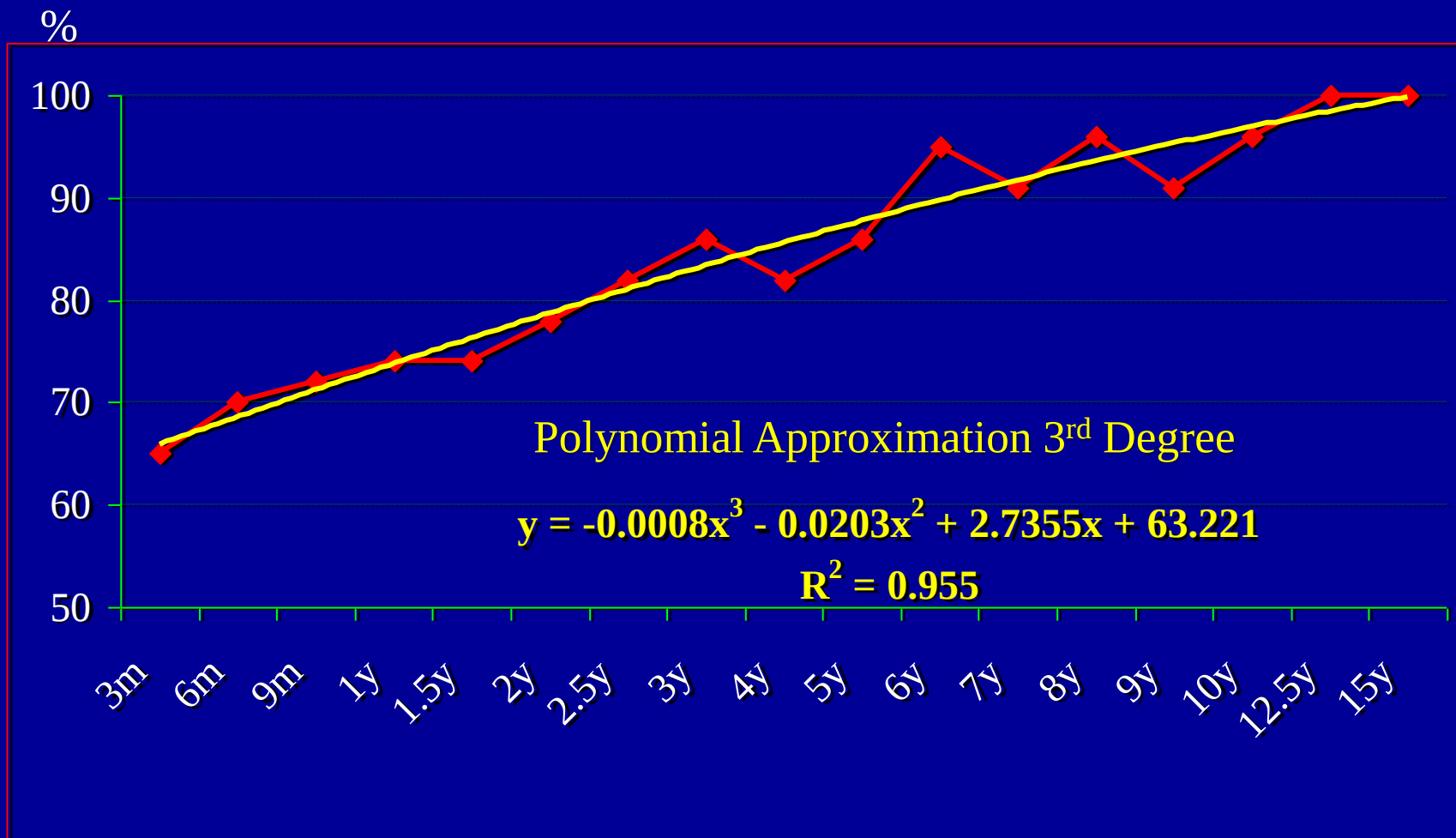
POSTERIOR UVEITIS

PCP + AZA



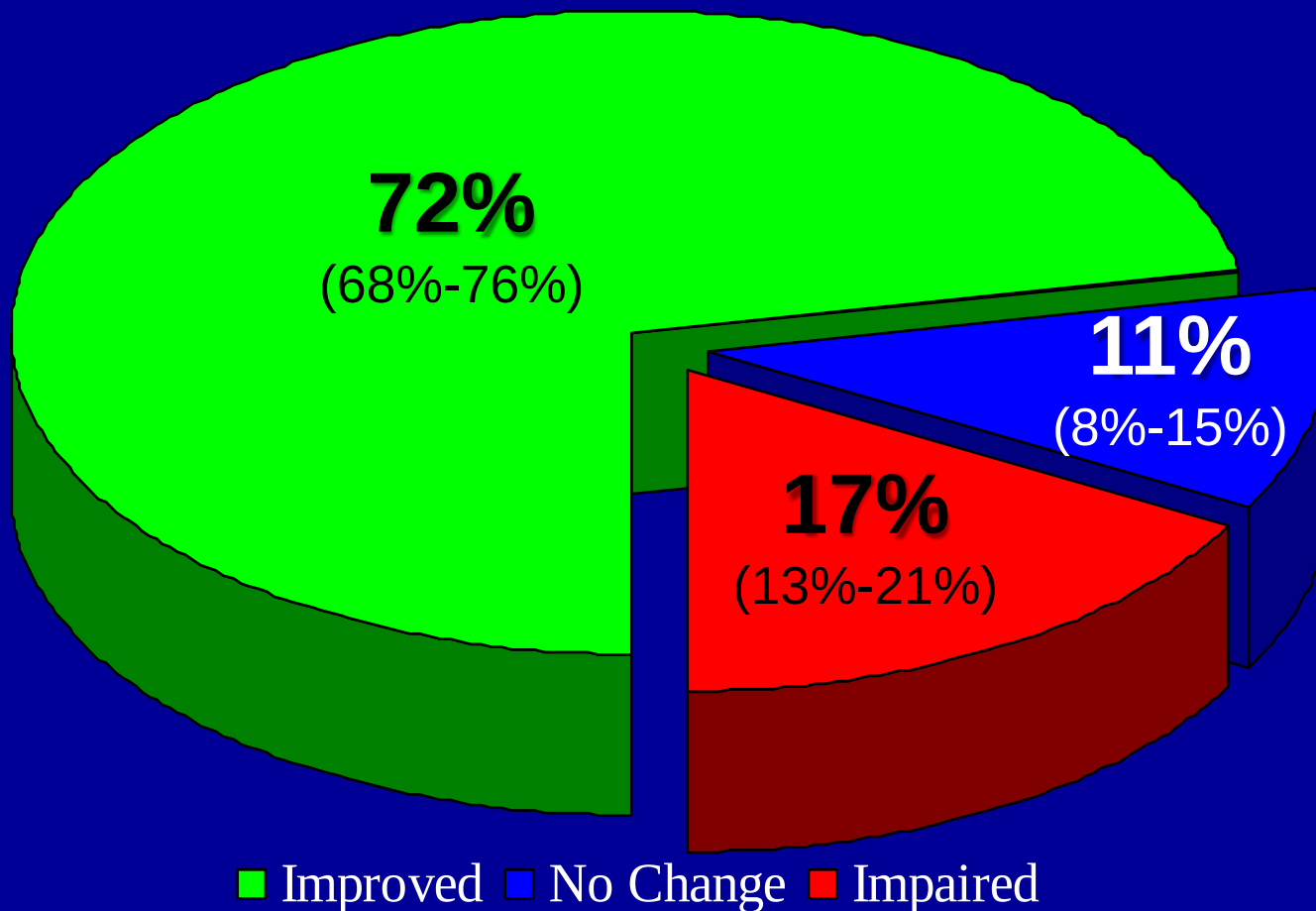
Longitudinal Study

Posterior Uveitis – % Improvement



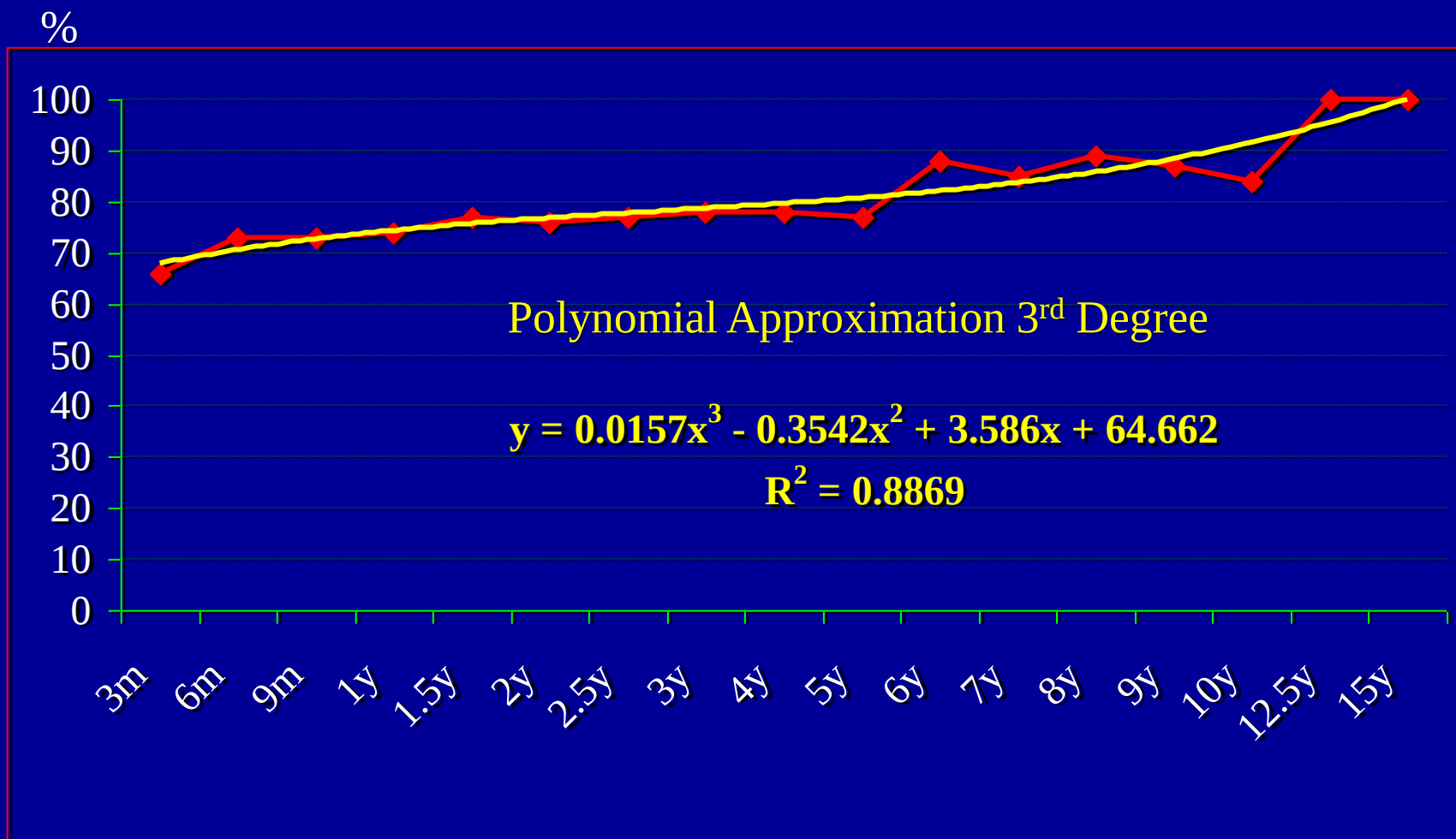
RETINAL VASCULITIS

PCP + AZA



Longitudinal Study

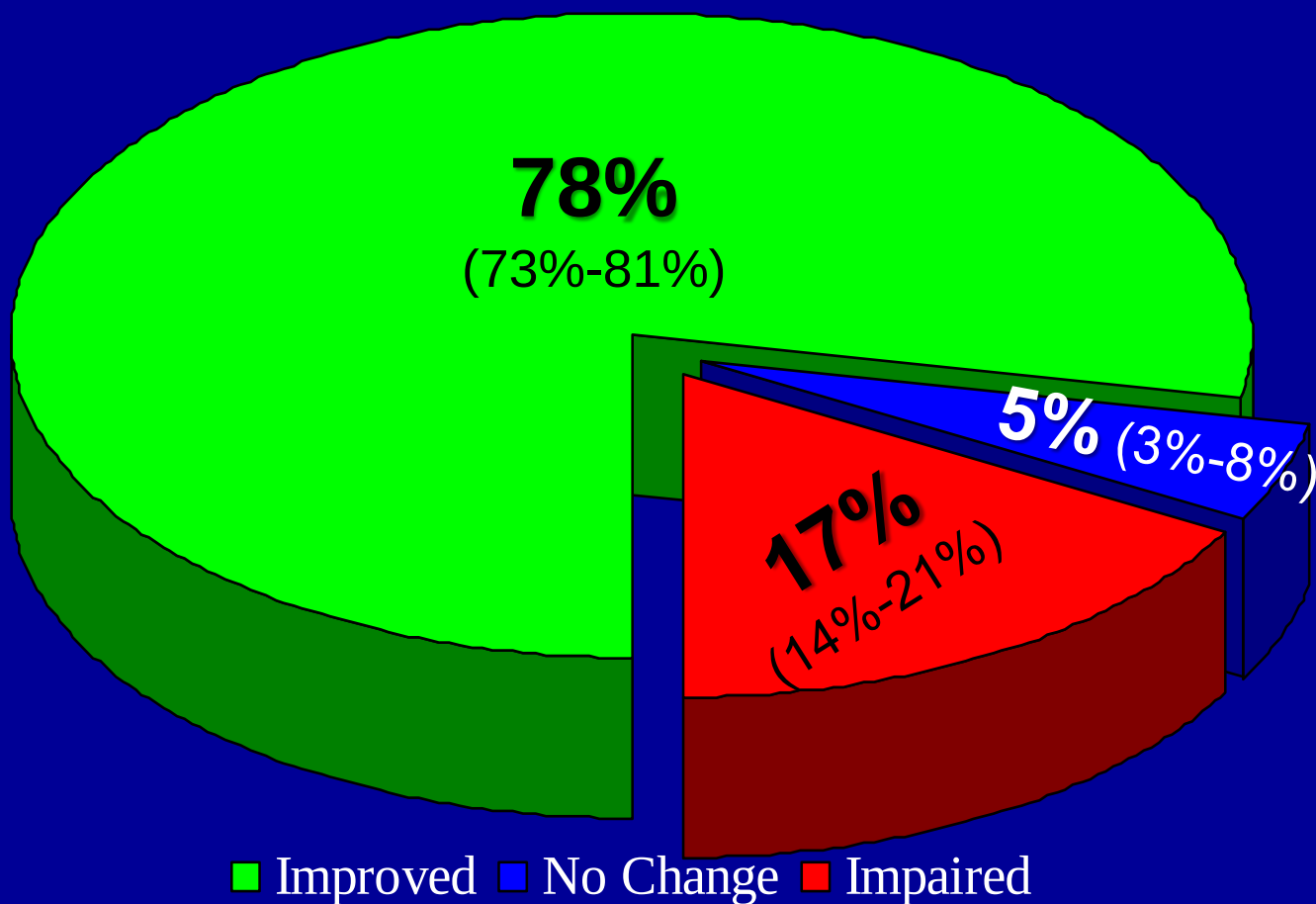
Retinal Vasculitis – % Improvement



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

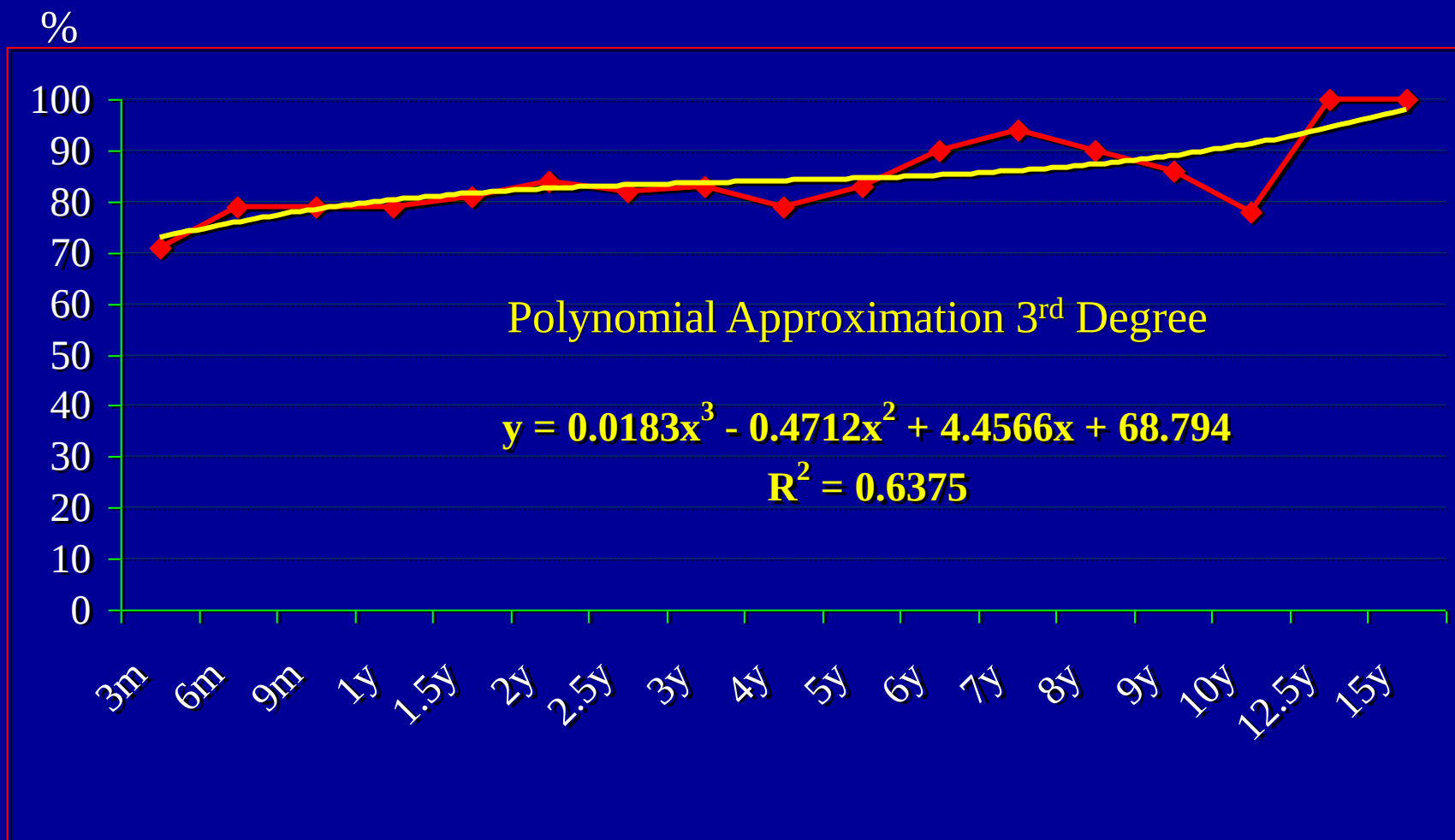
$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$

PCP + AZA



Longitudinal Study

$T_{\text{otal}} A_{\text{djusted}} D_{\text{isease}} A_{\text{ctivity}} I_{\text{ndex}} - \% \text{ Improvement}$



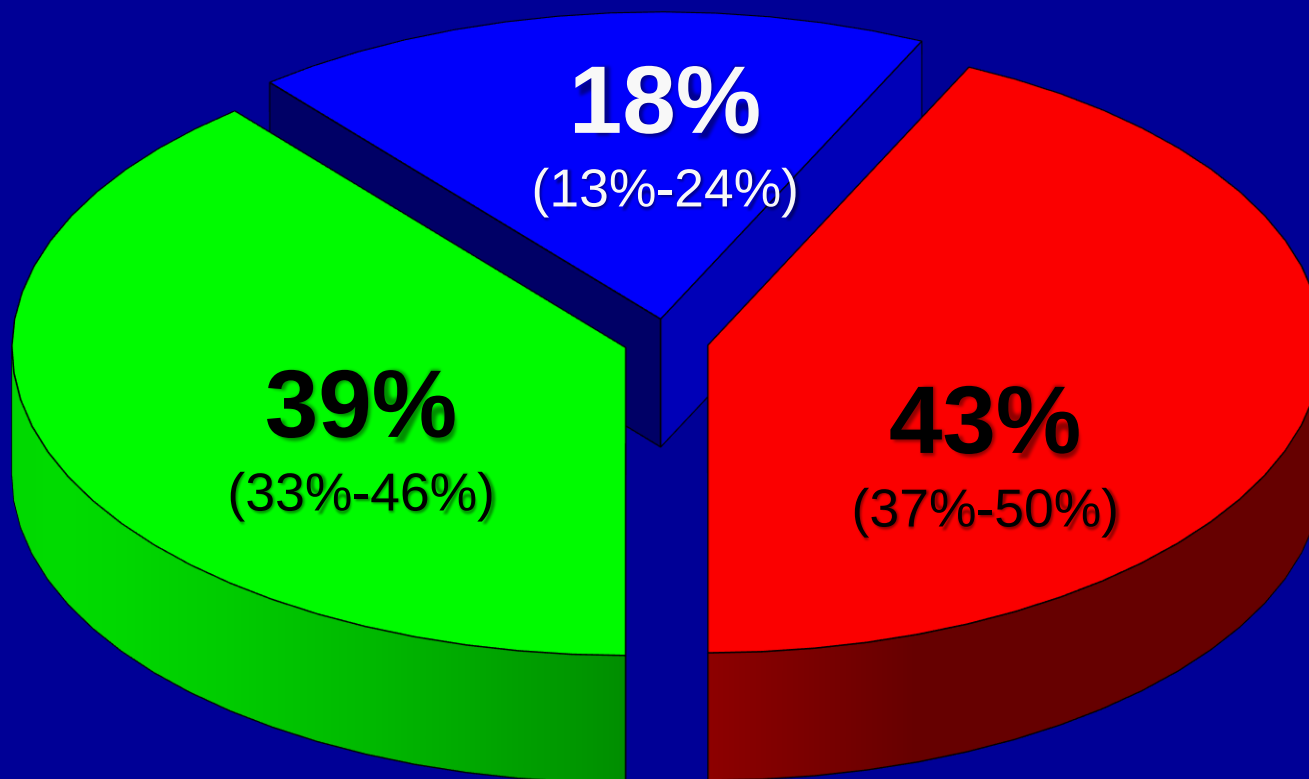
PULSE CYCLOPHOSPHAMIDE & METHOTREXATE

123 Patients

Longitudinal Study up to 15 Years

VISUAL ACUITY

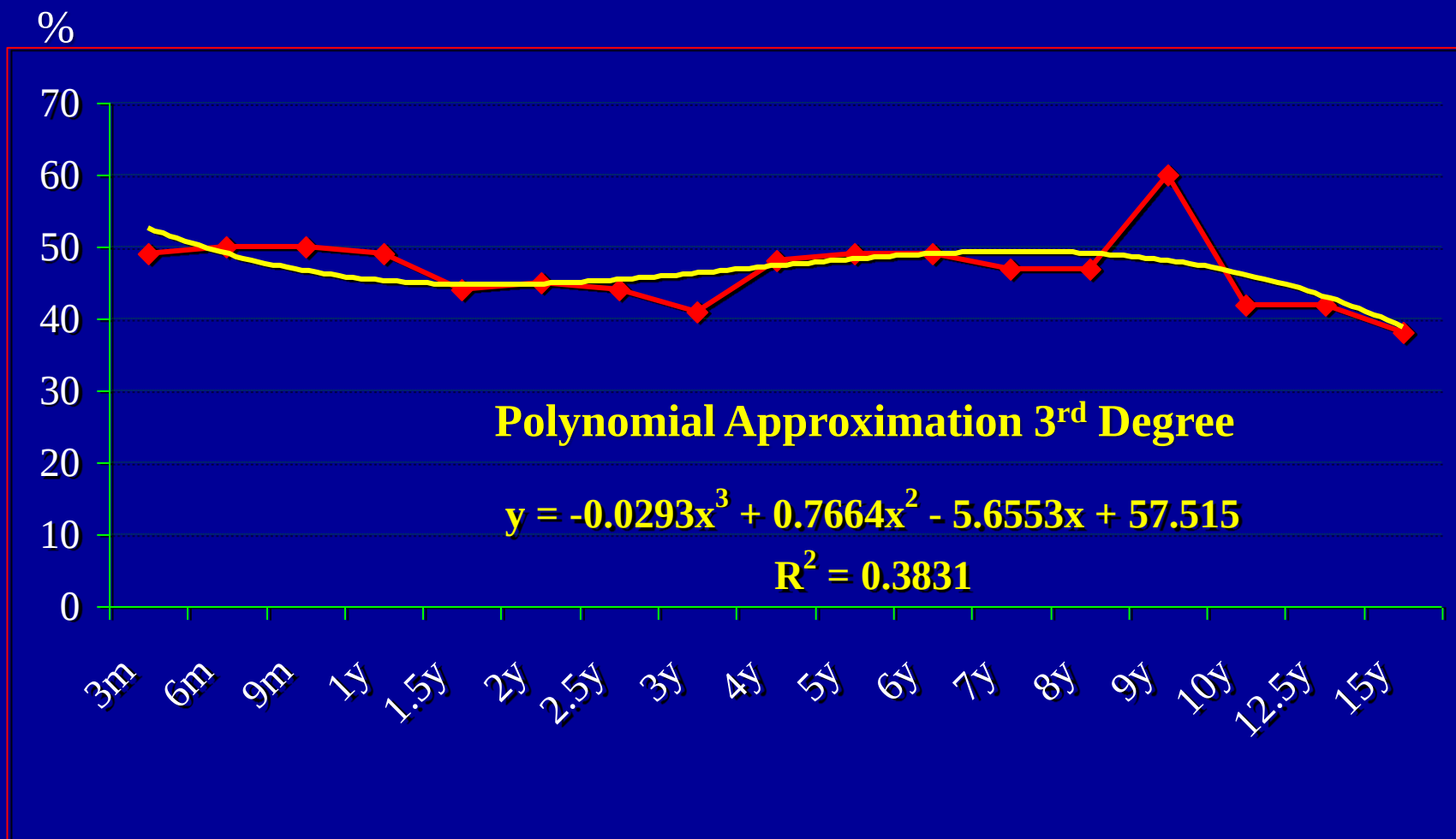
PCP - MTX



■ Improved ■ No Change ■ Impaired

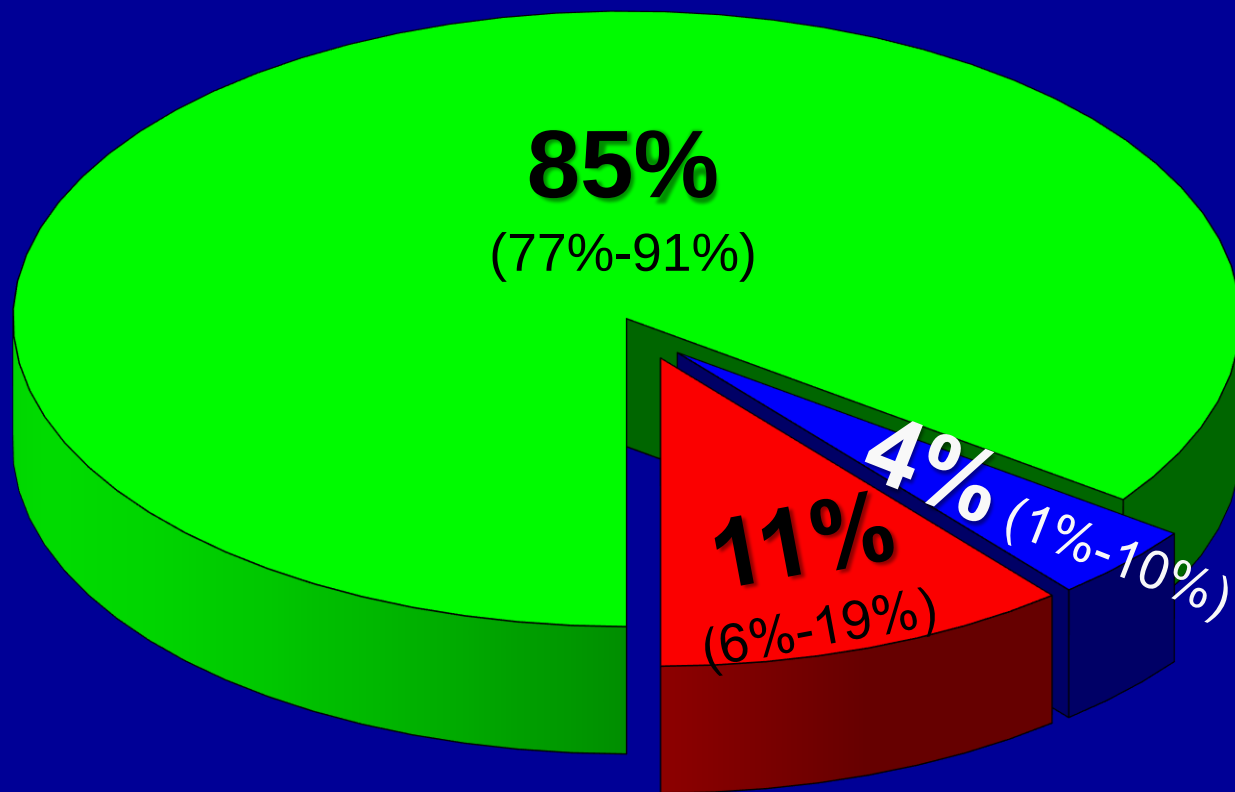
Longitudinal Study

Visual Acuity – % Improvement



ANTERIOR UVEITIS

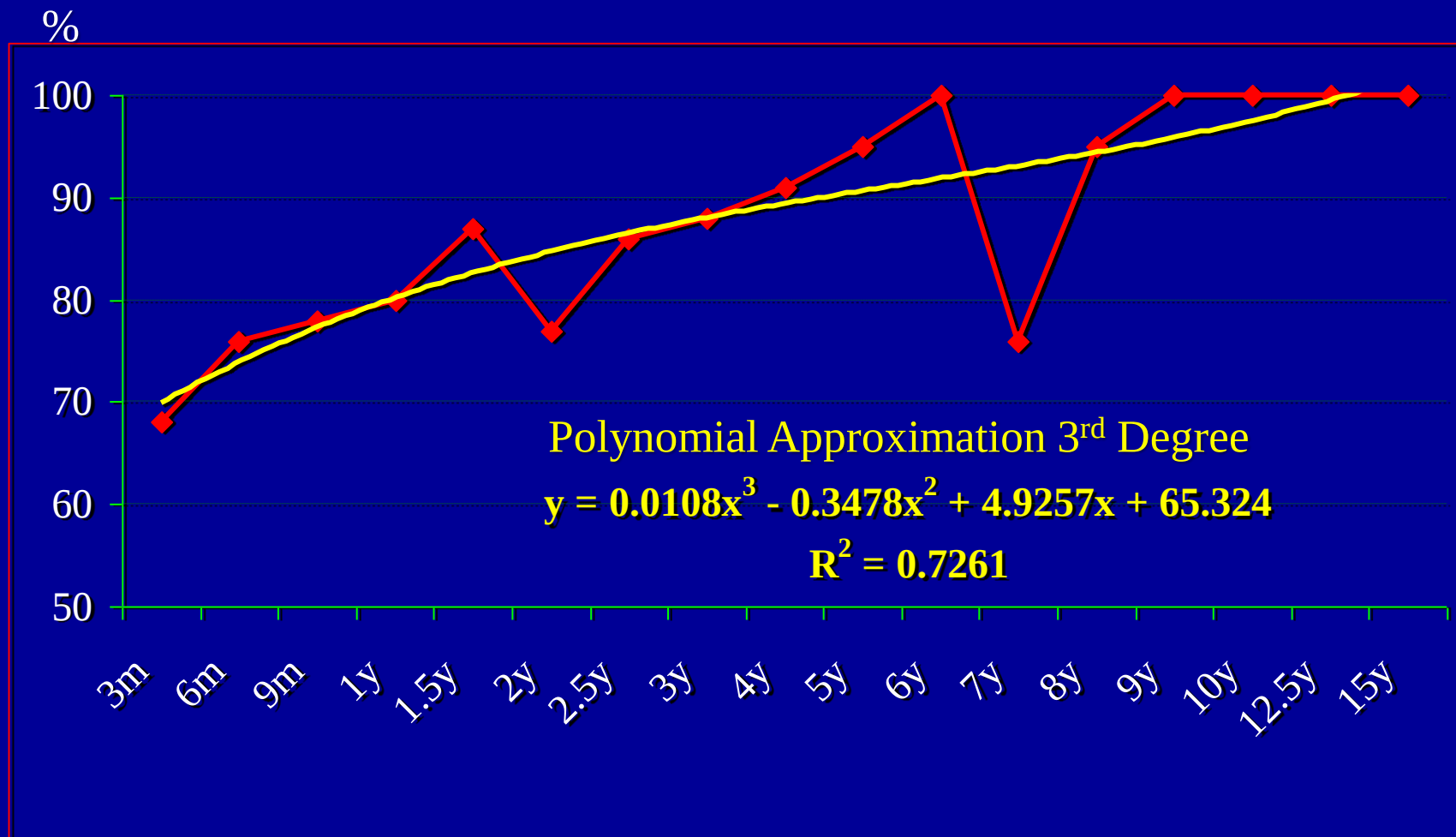
PCP - MTX



■ Improved ■ No Change ■ Impaired

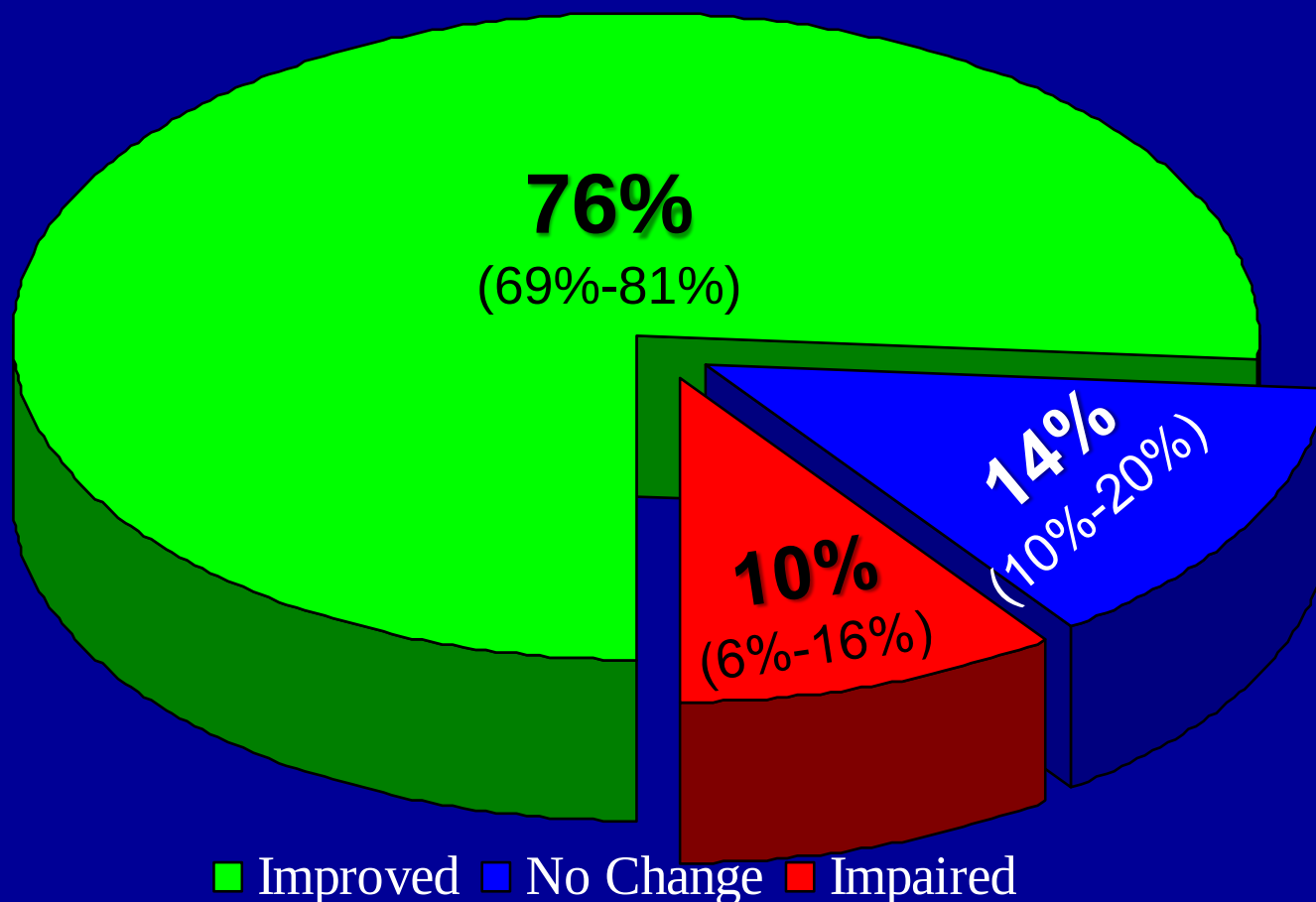
Longitudinal Study

Anterior Uveitis – % Improvement



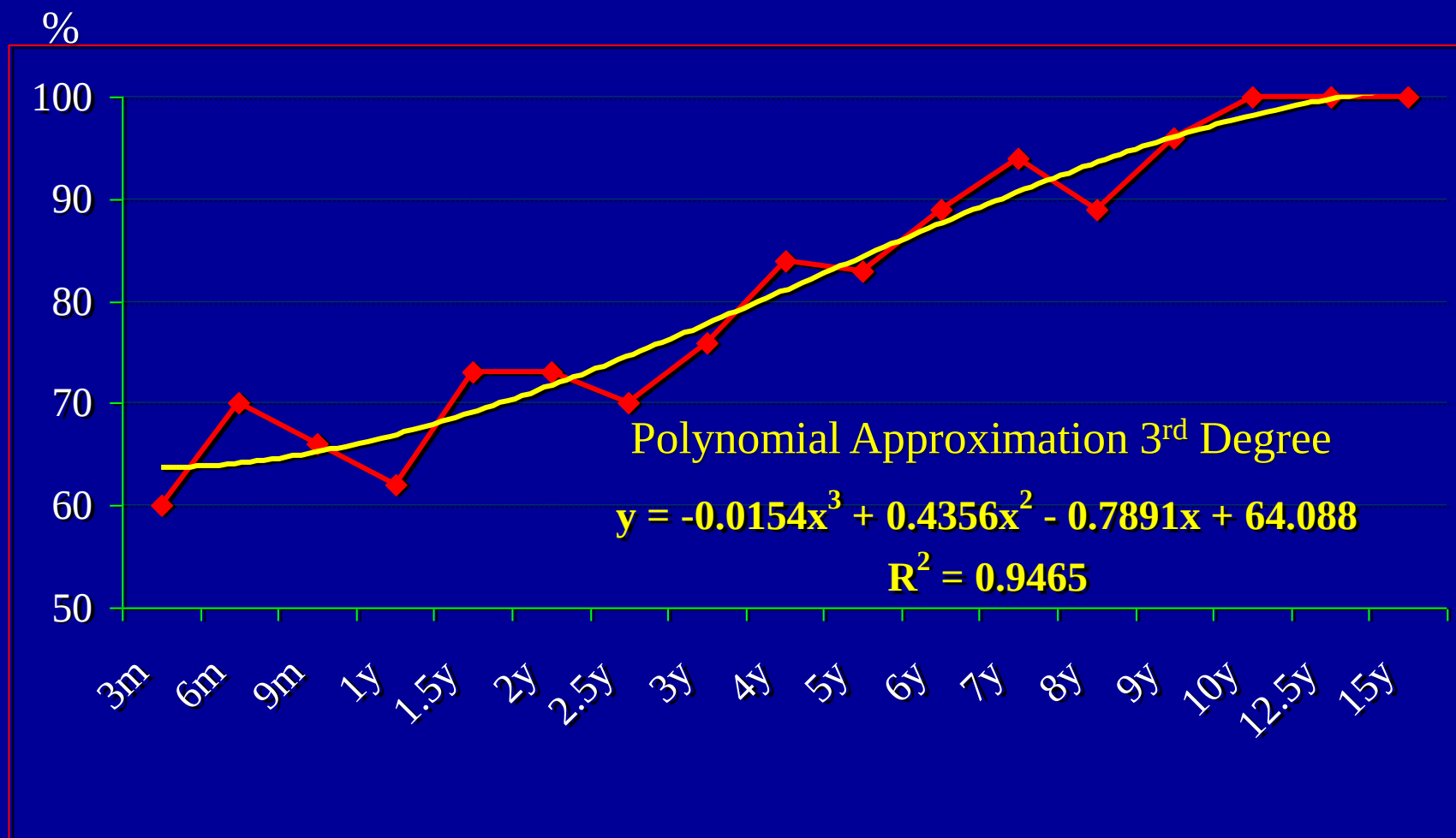
POSTERIOR UVEITIS

PCP - MTX



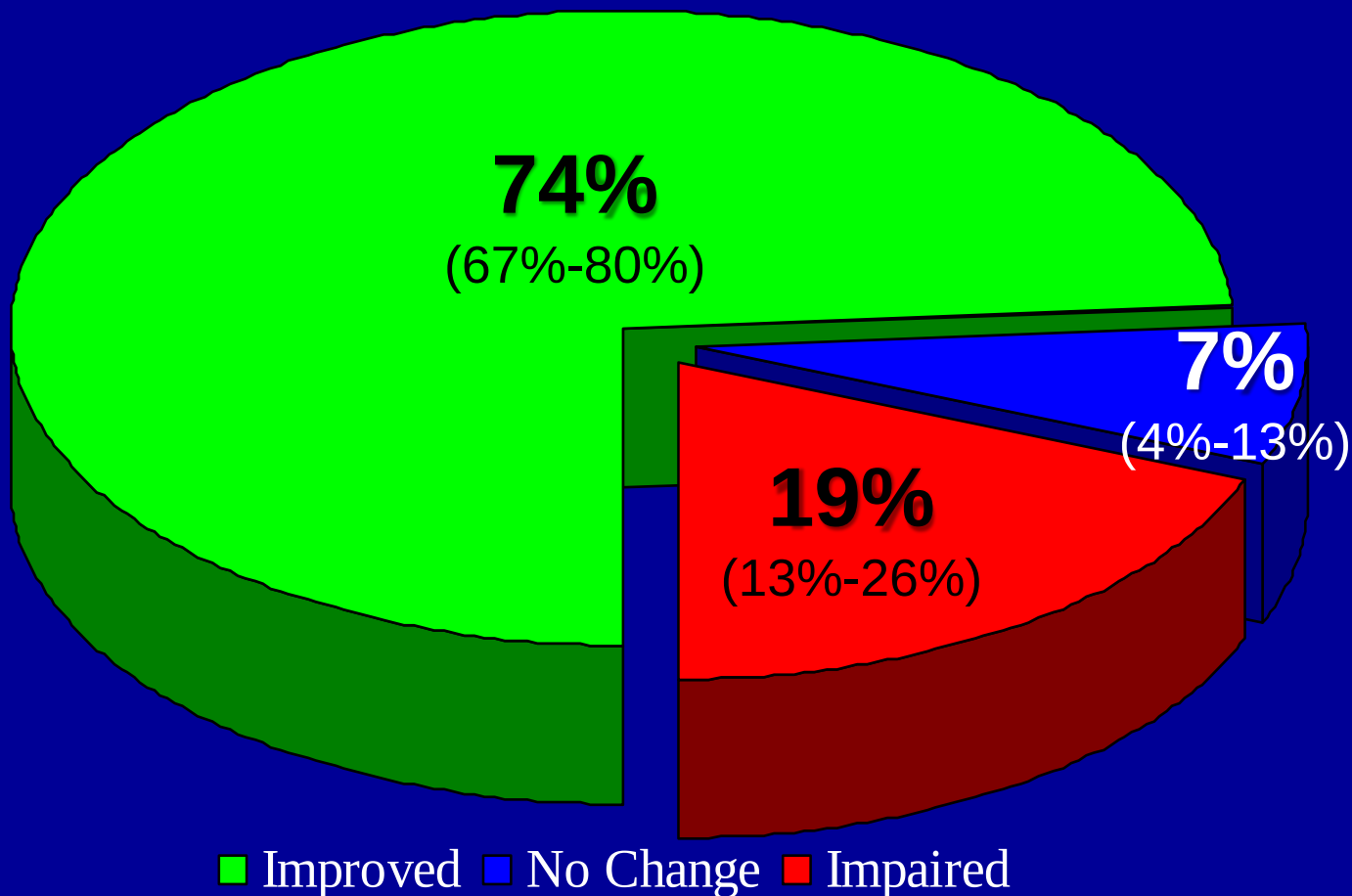
Longitudinal Study

Posterior Uveitis – % Improvement



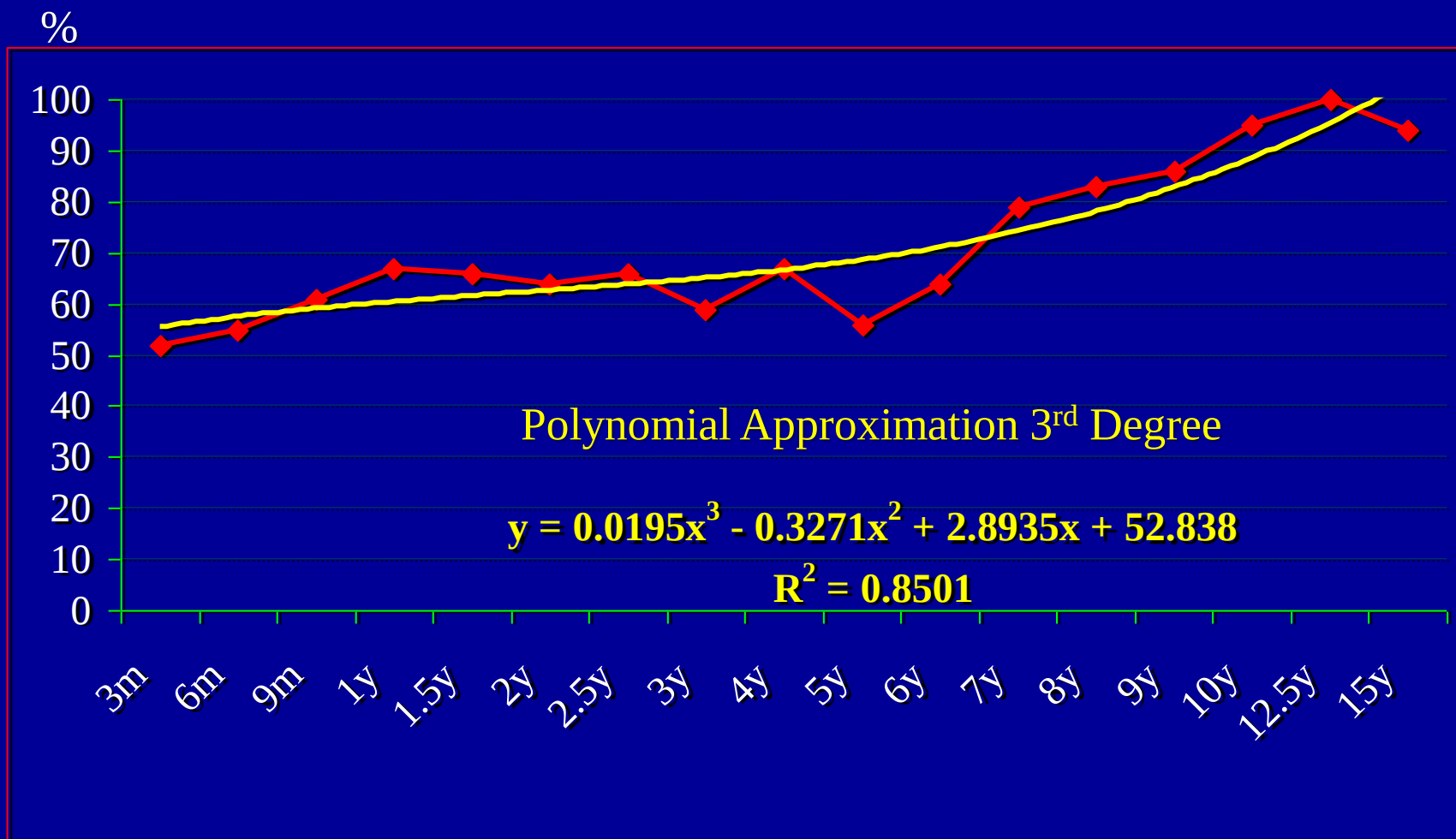
RETINAL VASCULITIS

PCP - MTX



Longitudinal Study

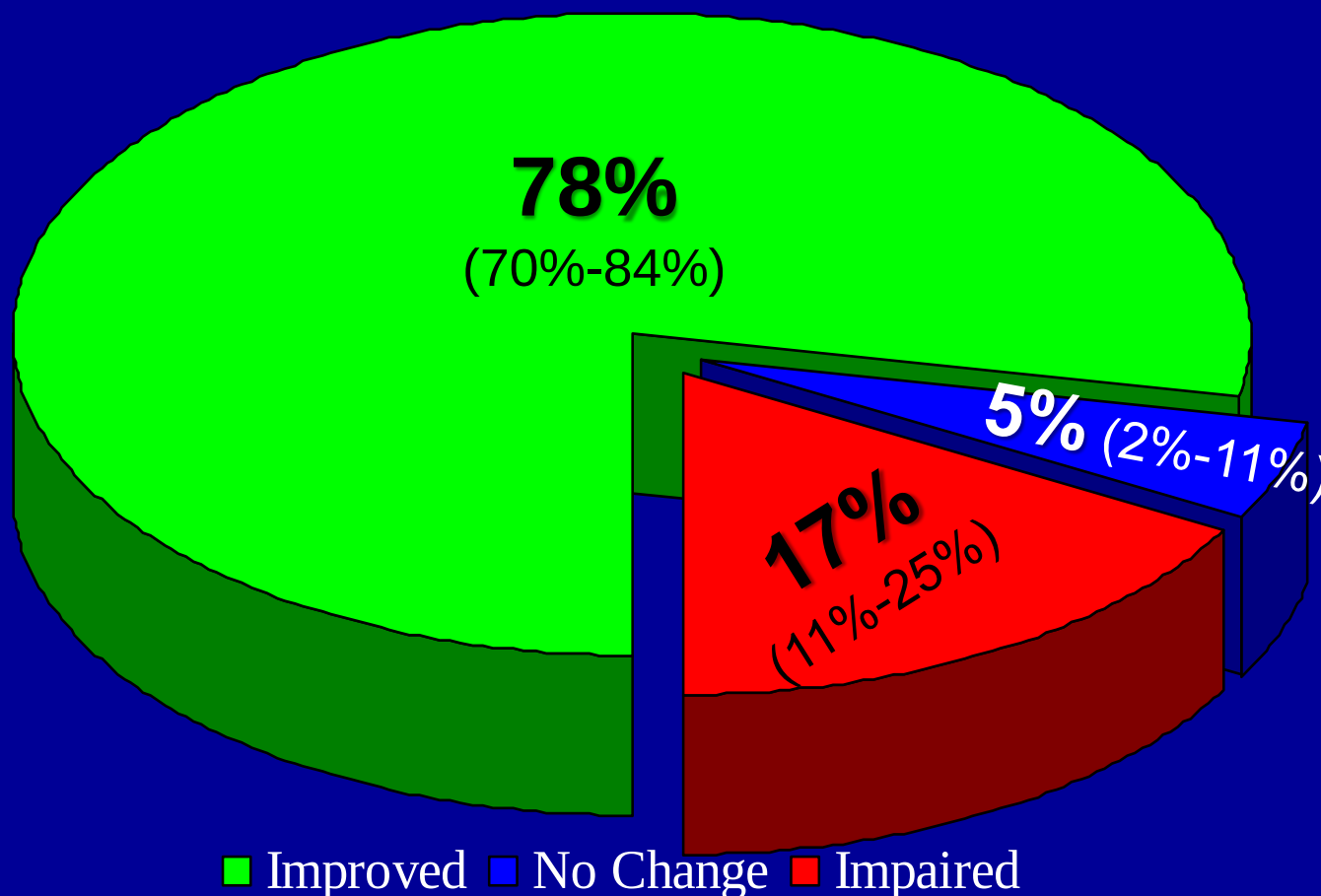
Retinal Vasculitis – % Improvement



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

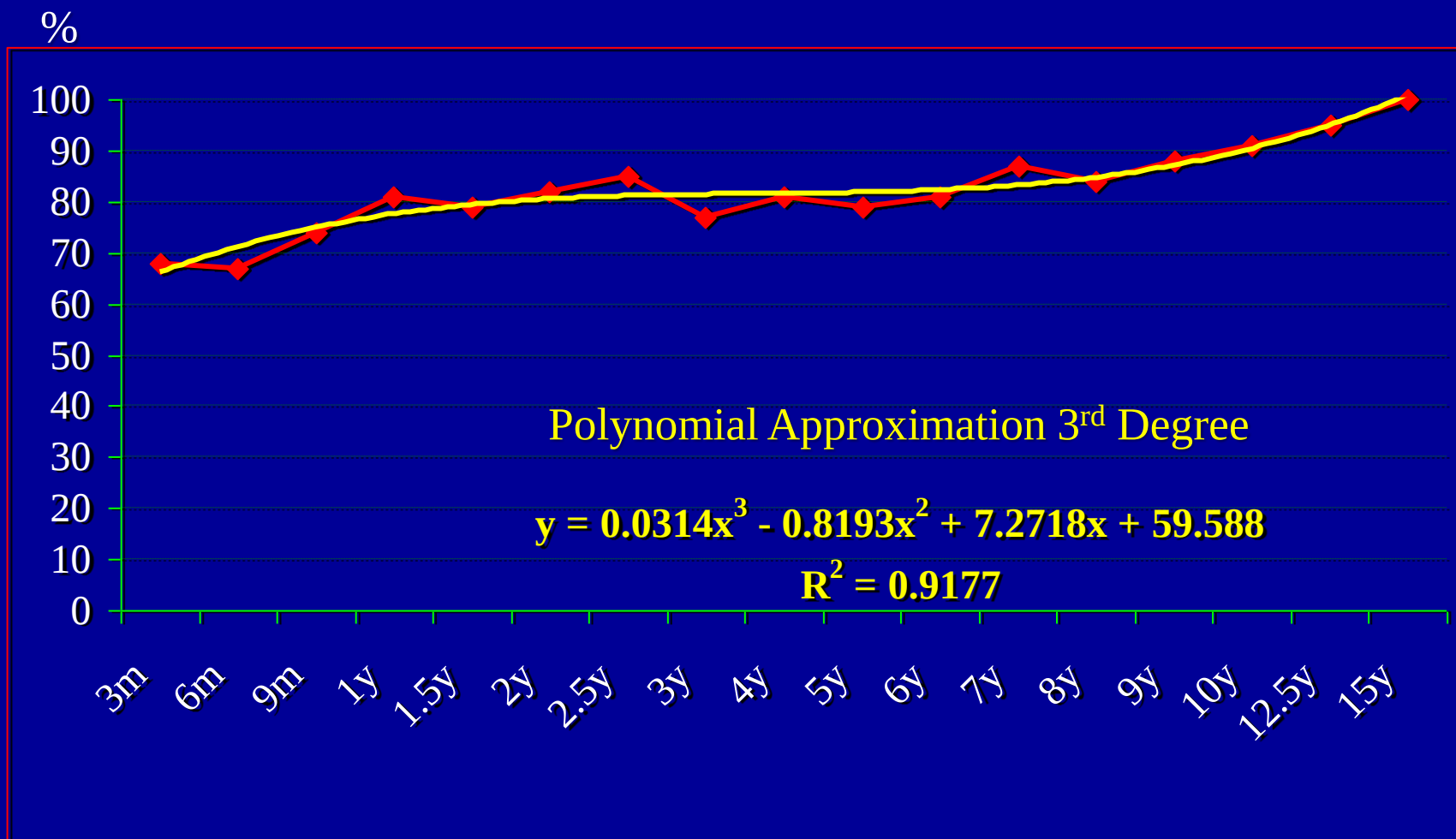
$$(AU \times 1) + (PU \times 2) + (RV \times 3) + [10 - (VA \times 2)]$$

PCP - MTX



Longitudinal Study

T_{total} A_{adjusted} D_{isease} A_{ctivity} I_{ndex} – % Improvement



مقایسه

مقایسه درصد بهتر شدن

<u>TADAI</u>	<u>واسکولیت رتین</u>	<u>اوئیت خلفی</u>	<u>اوئیت قدامی</u>	<u>دید</u>	<u>سایتوتوکسیک</u>
۷۳	۵۹	۷۶	۸۳	۴۷	کلرامبوسیل
۶۵	۵۷	۷۱	۸۶	۲۷	سیکلوسپورین
۷۲	۵۵	۷۶	۷۸	۴۸	متوترکسات
۷۷	۶۵	۷۲	۸۰	۴۱	آزاتیوپرین
۶۳	۵۰	۶۴	۶۴	۳۷	سایکلوفسفاماید
۷۸	۷۲	۷۶	۸۱	۴۵	PCP-AZA
۷۸	۷۴	۷۶	۸۵	۳۹	PCP-MTX

ALL CYTOTOXICS

1797 Patients

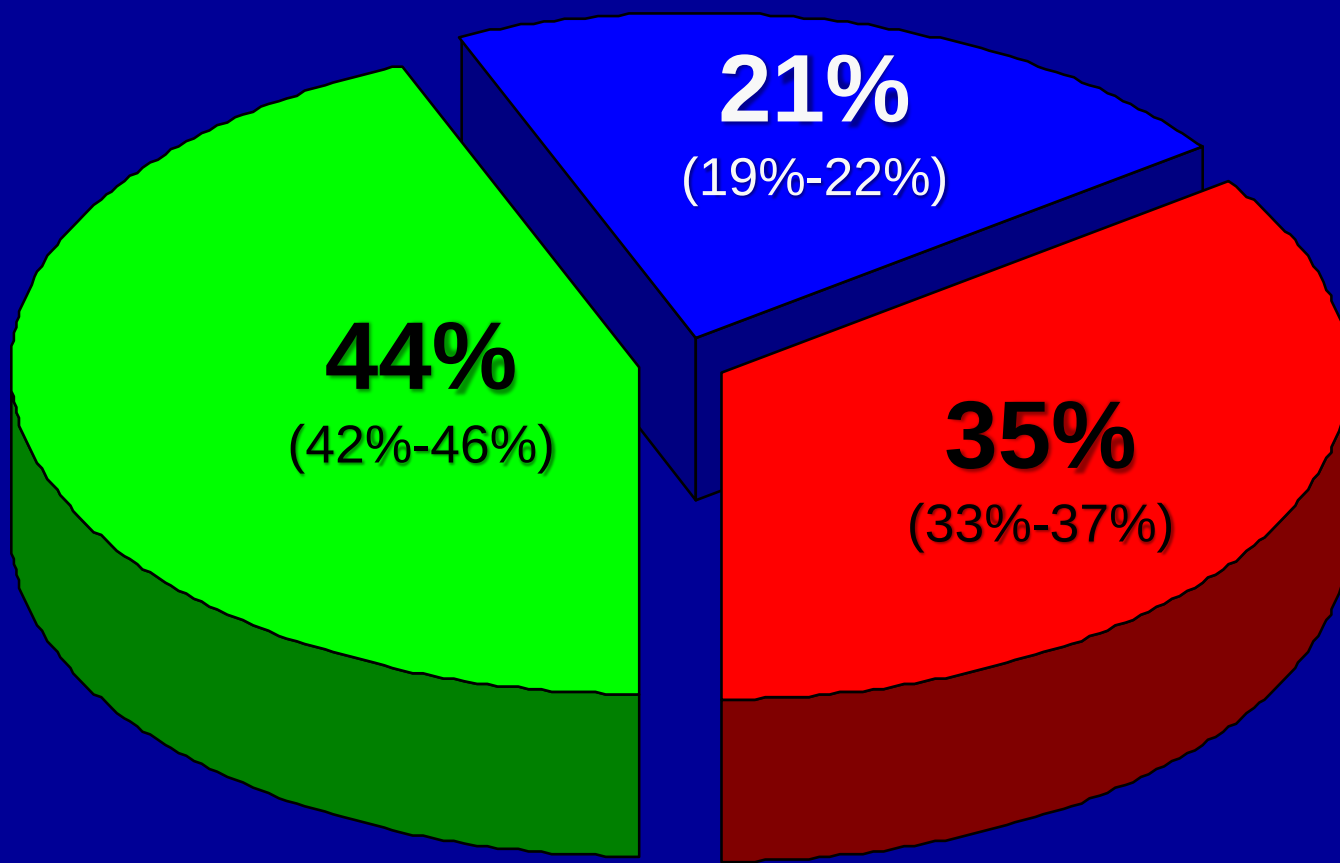
Longitudinal Study Up To 30 Years

THERAPEUTIC PROTOCOLS

- Azathioprine
- Chlorambucil
- Cyclosporine
- Methotrexate
- Pulse Cyclophosphamide
- PCP – MTX
- PCP – AZA

VISUAL ACUITY

Eyes Overall Results



■ Improved ■ No Change ■ Impaired

VISUAL ACUITY

% Eyes Improved – Longitudinal Study of 30 Years

%

60

50

40

30

20

10

0

3m

1y

2.5y

5y

7y

10y

20

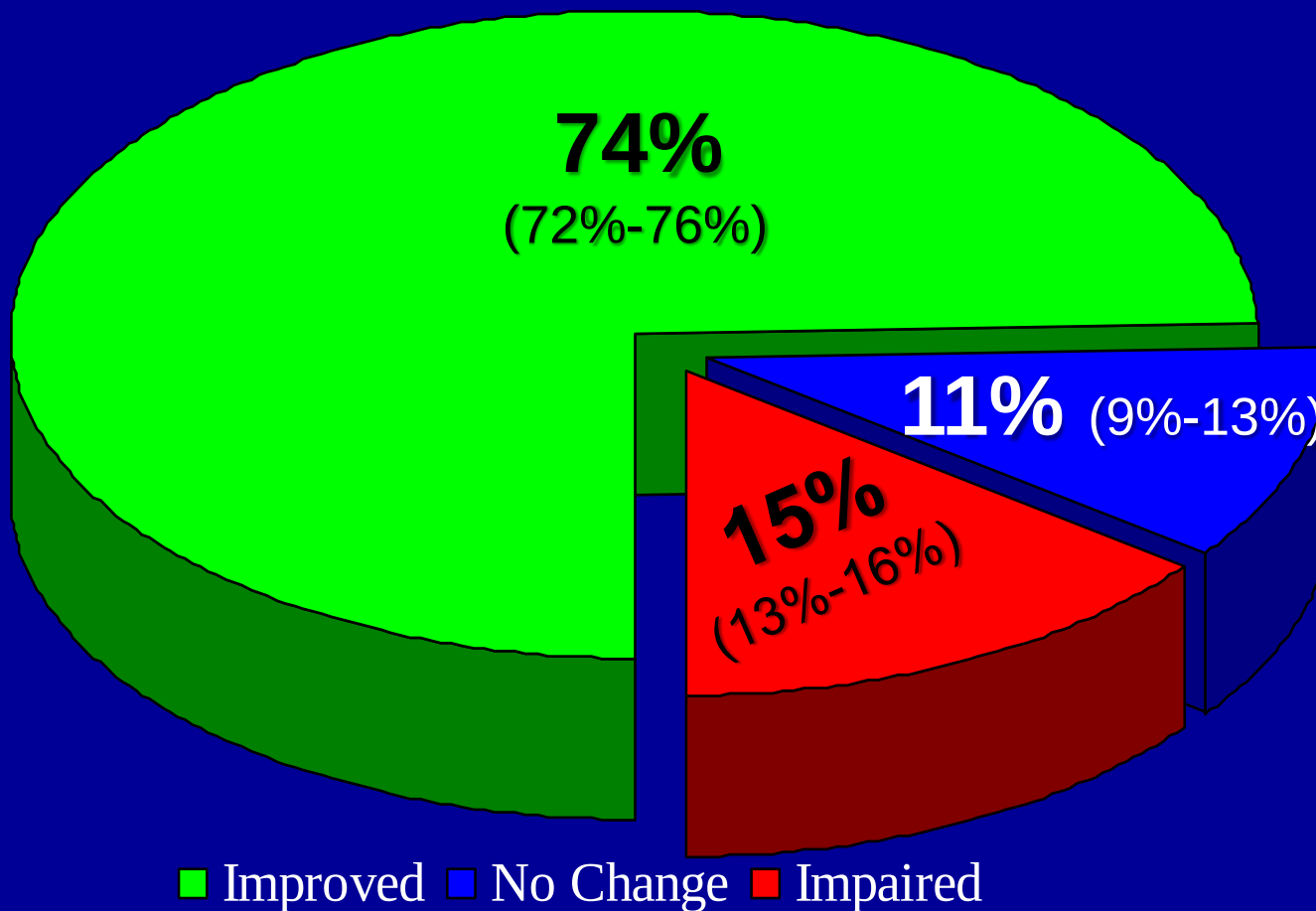
Polynomial Approximation 3rd Degree

$$y = 0.0089x^3 - 0.2583x^2 + 1.0759x + 53.102$$

$$R^2 = 0.7161$$

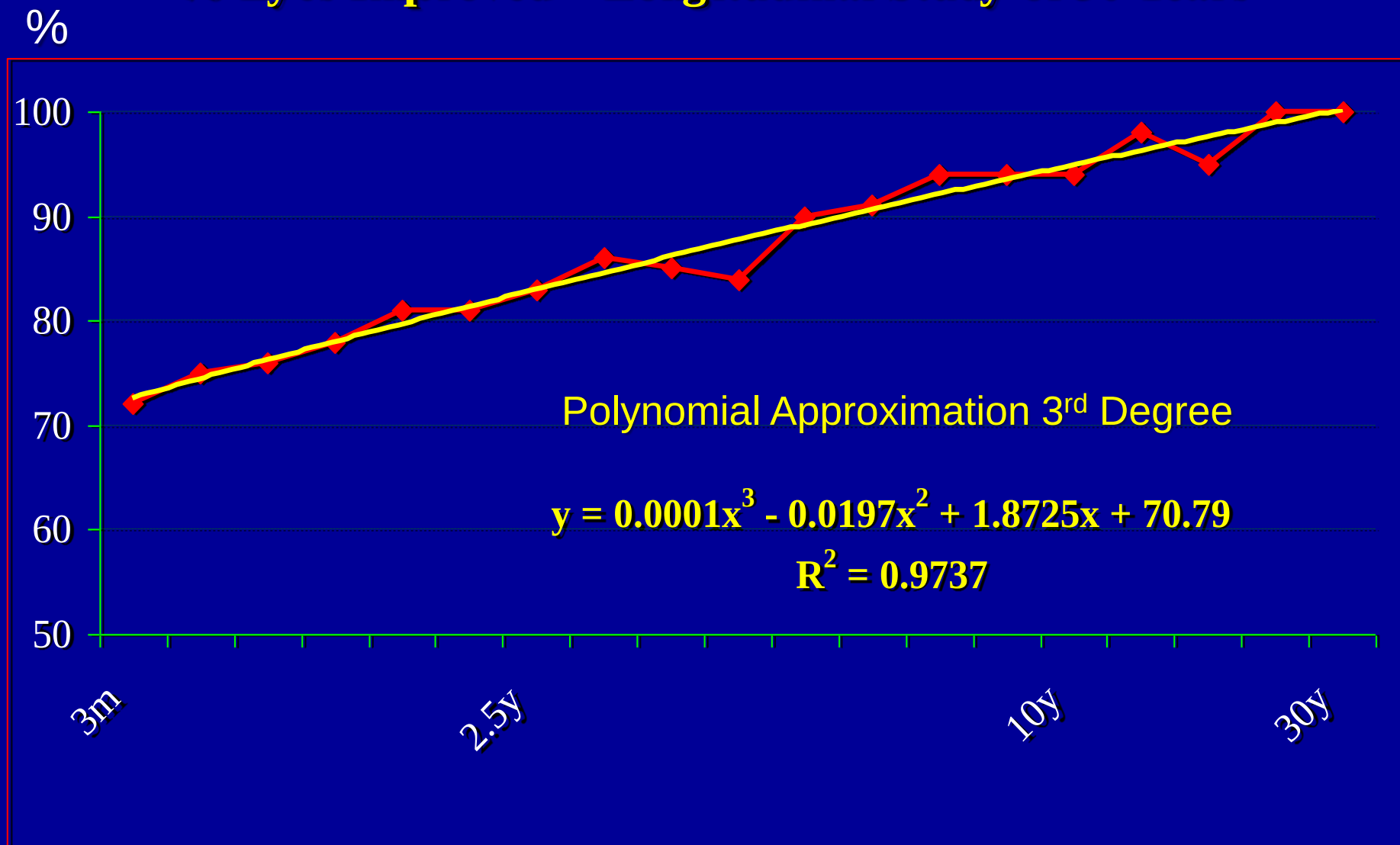
ANTERIOR UVEITIS

Eyes Overall Results



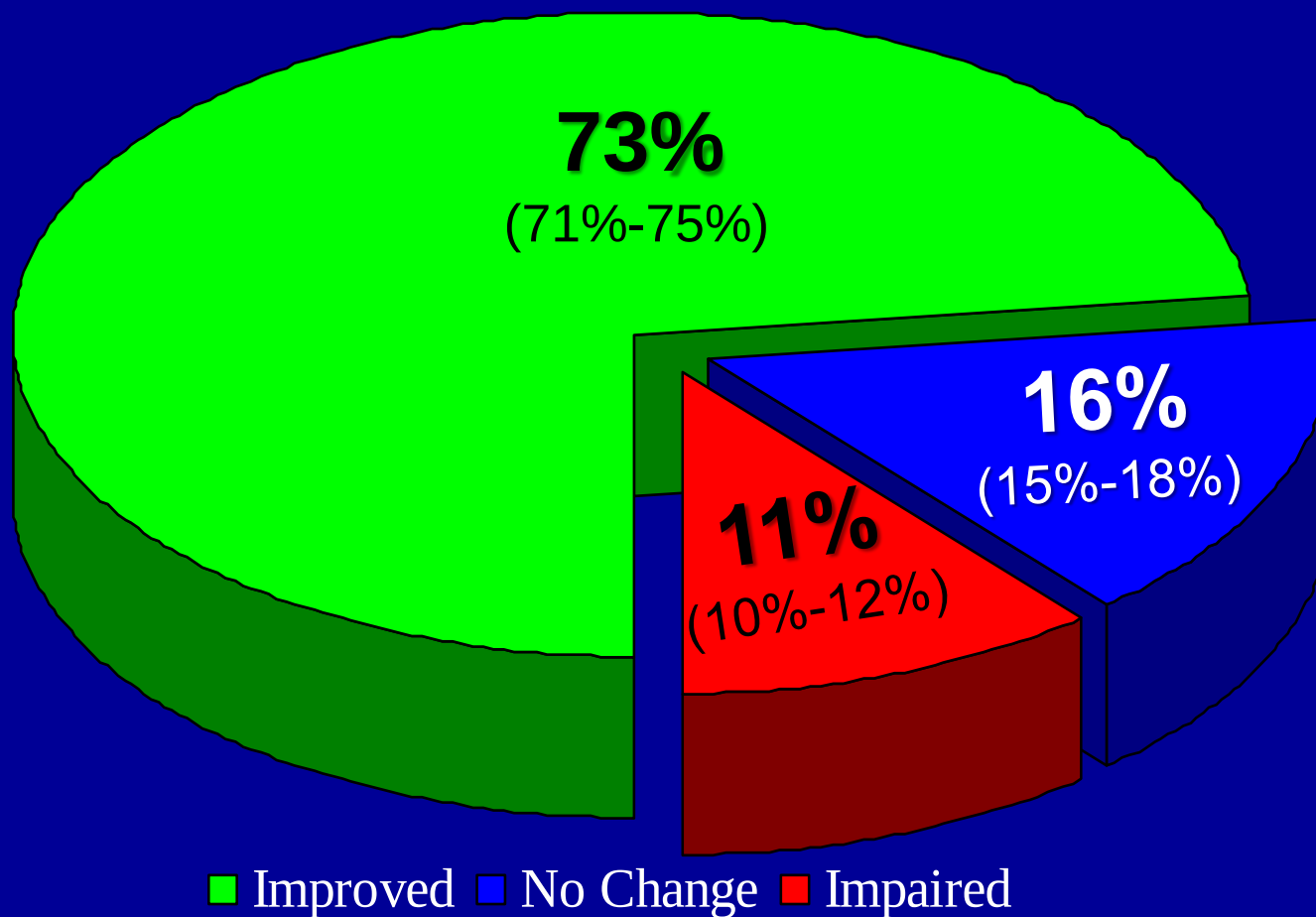
ANTERIOR UVEITIS

% Eyes Improved – Longitudinal Study of 30 Years



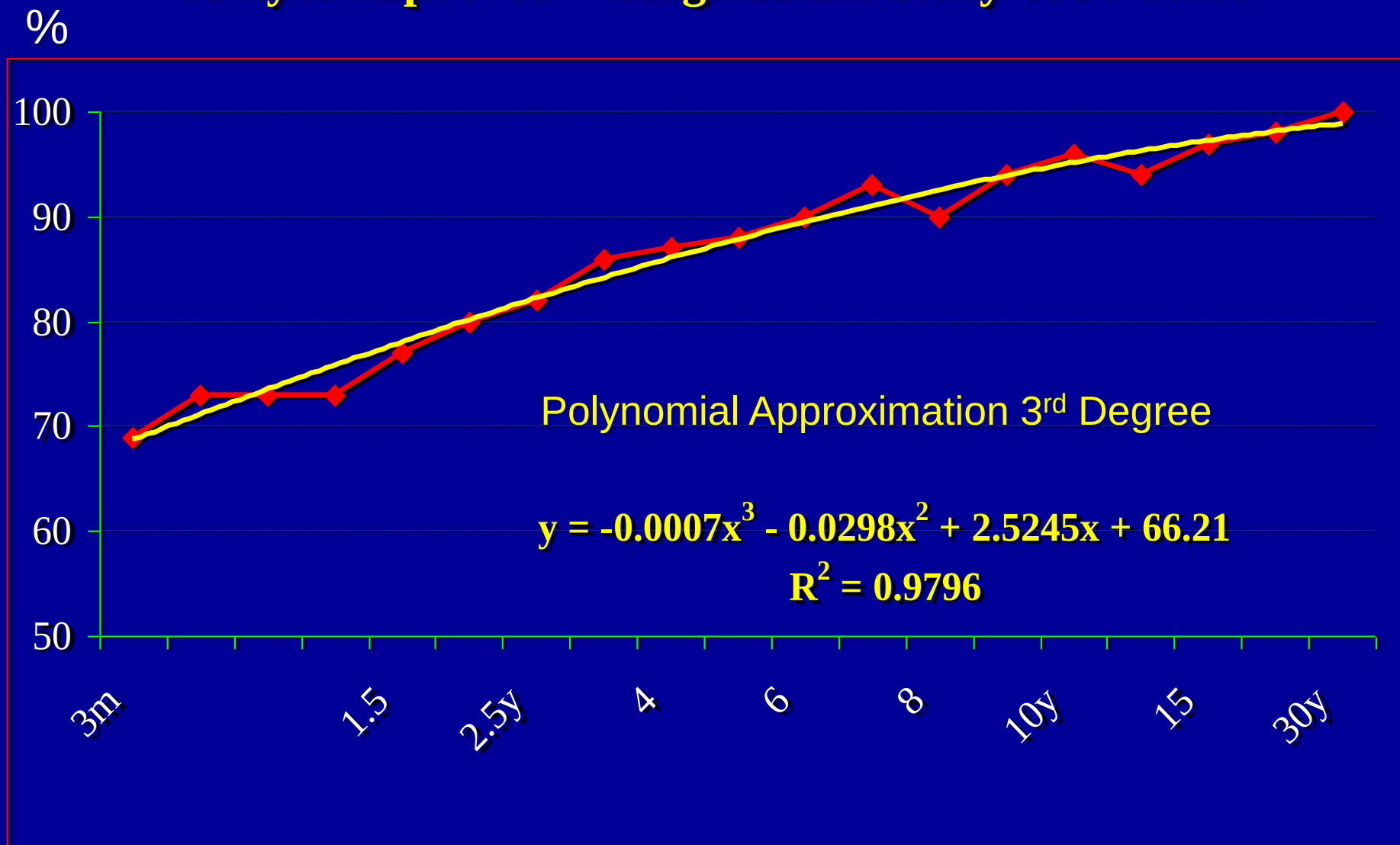
POSTERIOR UVEITIS

Eyes Overall Results



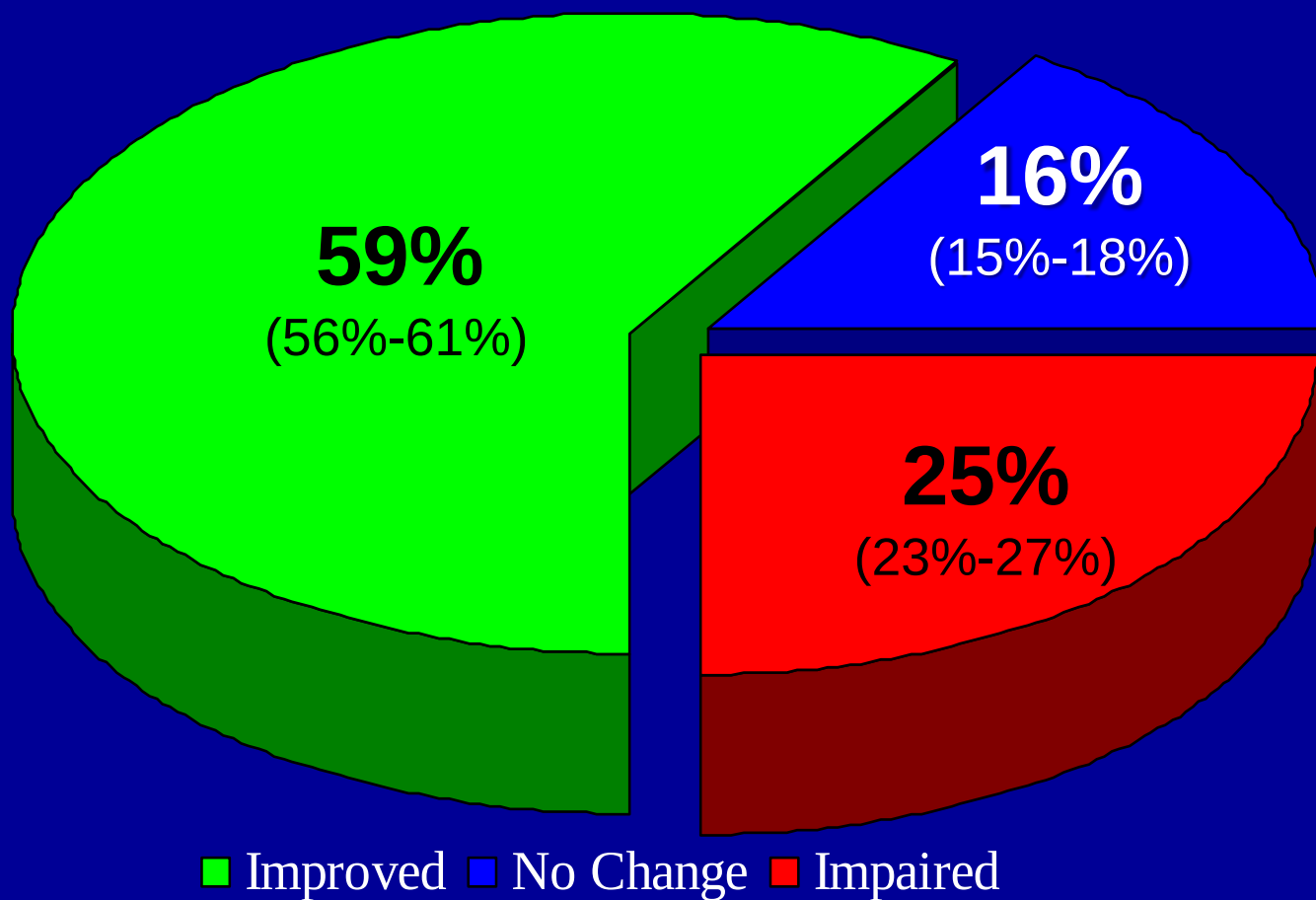
POSTERIOR UVEITIS

% Eyes Improved – Longitudinal Study of 30 Years



RETINAL VASCULITIS

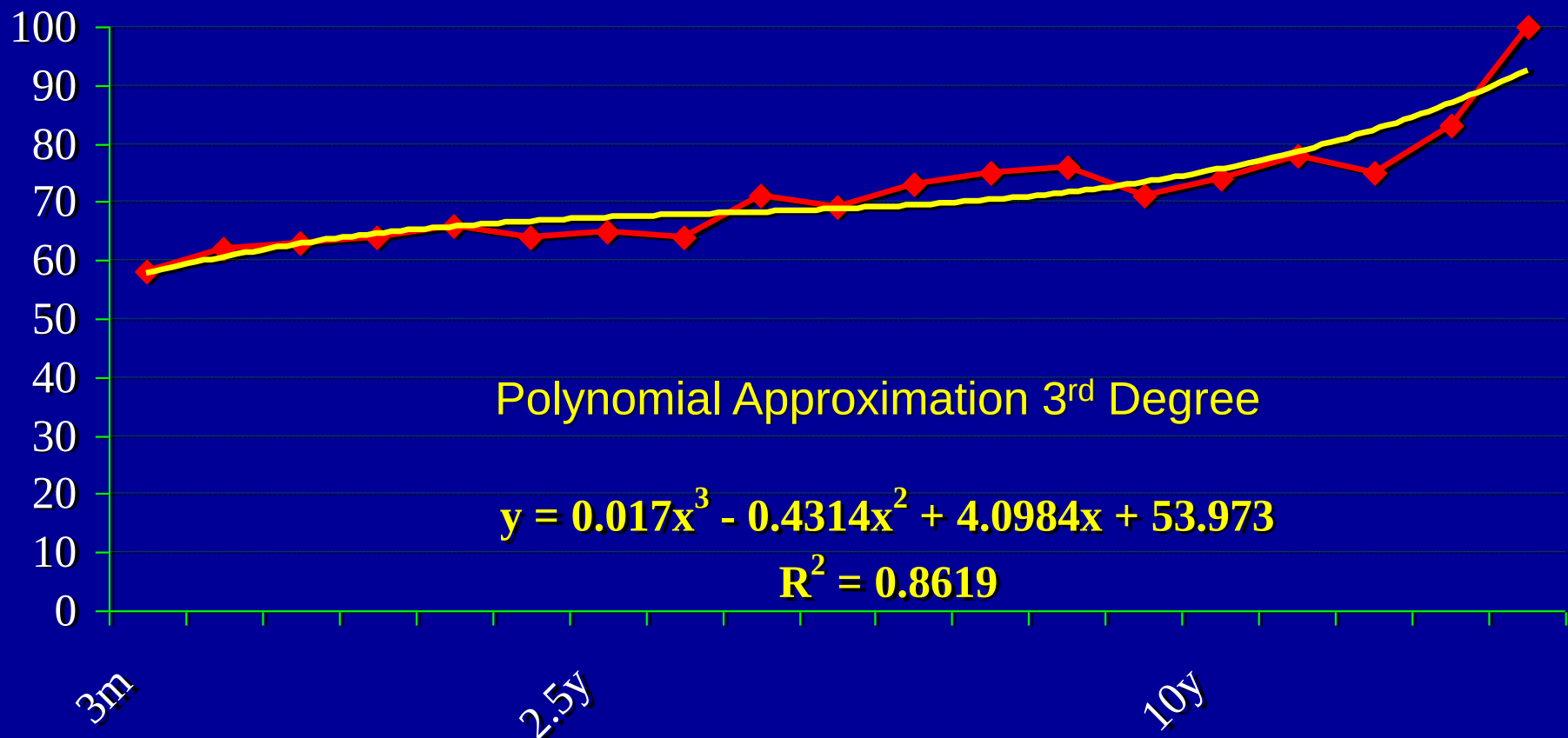
Eyes Overall Results



RETINAL VASCULITIS

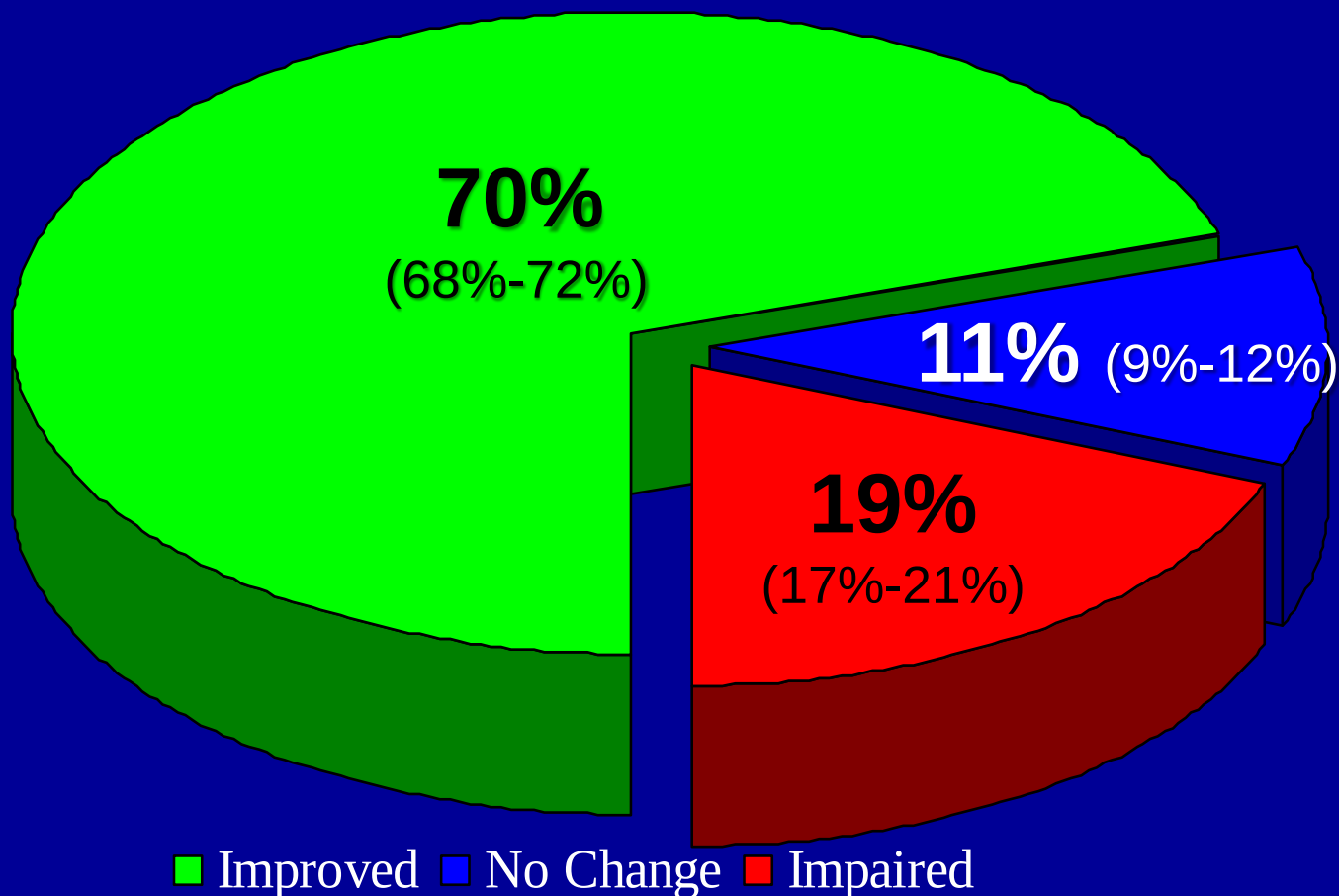
% Eyes Improved – Longitudinal Study of 30 Years

%



TOTAL ADJUSTED DISEASE ACTIVITY INDEX

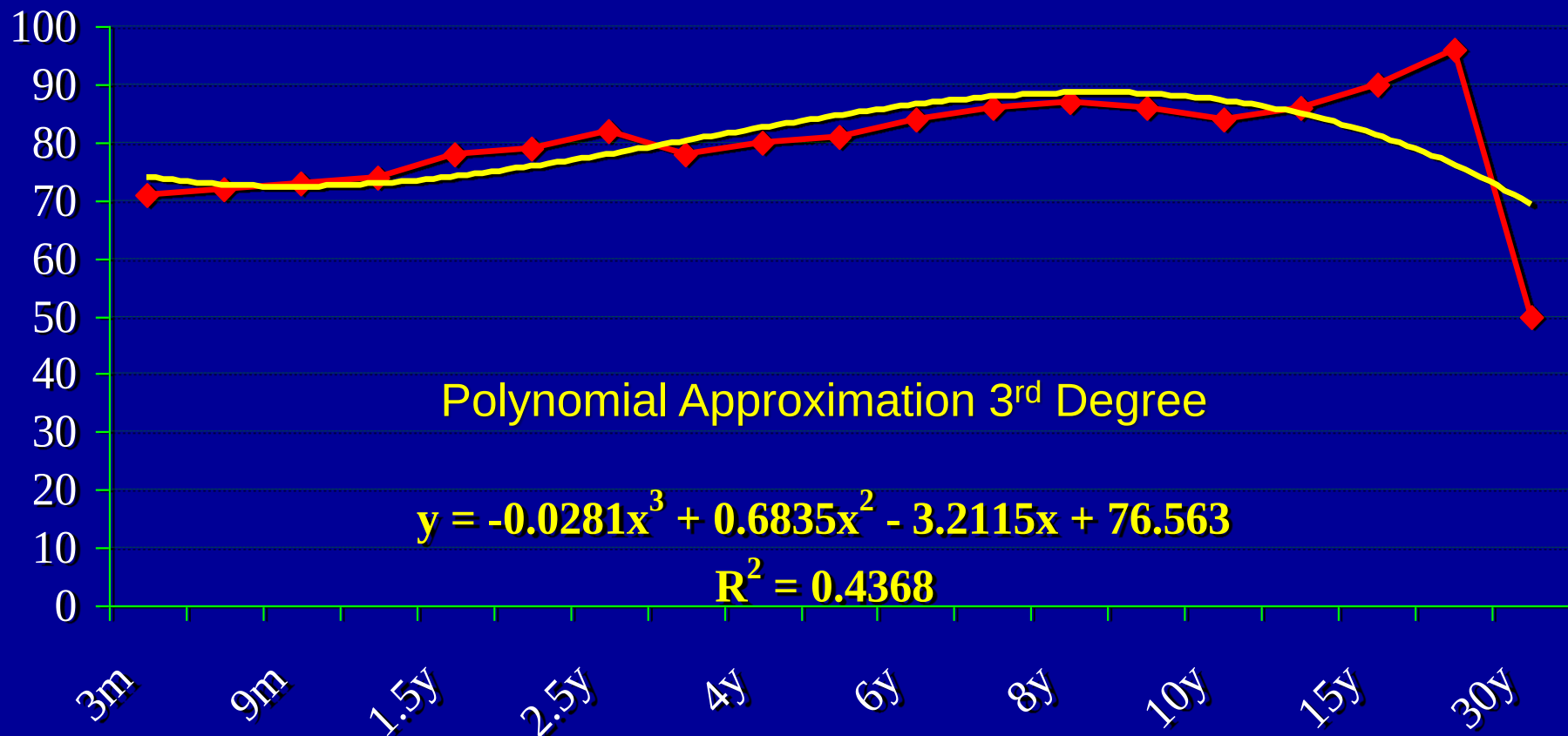
Patients Overall Results



Total Adjusted Disease Activity Index

% Patients Improved – Longitudinal Study of 30 Years

%



مقایسه درصد بهتر شدن

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۷۸	۷۲	۷۶	۸۱	۴۵	PCP-AZA
۷۸	۷۴	۷۶	۸۵	۳۹	PCP-MTX
۷۰	۵۹	۷۳	۷۴	۴۴	همه با هم

Ben Ezra, British J Ophthalmol 1986; 70: 589-592

- از بین رفتن دید مفید در ۷۴٪ چشم ها
- مطالعه تا ۱۰ سال بعد از شروع درگیری در ۴۹ بیمار

در مطالعه ما

- از بین رفتن دید مفید در ۱۳/۵٪ چشم ها (۸٪ کوری حقیقی)
- مطالعه تا ۳۰ سال بعد از شروع درمان در ۱۷۹۷ بیمار

یازدهمین کنگره سالیانه انجمن روماتولوژی ایران

نتیجه

داروهای سایتوتوکسیک

- خط اول درمان
- بکار بردن آسان
- تاثیر پذیری در طول المدت
- کم خطر در مصرف طولانی
- قیمت ارزان
- ۳۰۰ برابر ارزانتر از داروهای بیولوژیک

BIOLOGIC AGENTS

INTERFERON- α

OCULAR LESIONS

Best Results

INTERFERON- α

1.	Alposi	11	Eyes	2002, Arch Dermatol
2.	Kotter	94	“	2003, Brit J Ophthalmol
3.	Tugal-Tuktun	88	“	2006, Arch Clin Exp Ophthalmol
4.	Deuter	15	“	2004, Ophthalmologe (German)
5.	Bodaghi	38	“	2007, Brit J Ophthalmol
6.	Kreuse	79	“	2008, J Rheumatol
7.	Deuter	96	“	2010, Arthritis Rheum
8.	Onal	68	“	2011, Archives Ophthalmol

META-ANALYSIS

489 Eyes – Mean Follow-up 28 months
After Adjustment
Mean Visual Acuity

INTERFERON- α

Mean Visual Acuity

	<u>%</u>
• Improvement	60
• Stabilization	30
• Aggravation	10

INTERFERON- α

Side Effects (Adjusted Mean) - 284 Patients

- Flue Like Syndrome 98%
- Alopecia 13
- Depression/Psychosis 21
- Thyroiditis 4
- Leukopenia 17
- Others 34

Anti TNF- α

ETANERCEPT

- Soluble Receptor for TNF- α
- Ocular Lesions Melikoglu 2002
 - 10 Patients, Open Study, 6 Months
 - VA improved (not statistically significant)

ETANERCEPT

Zhang et al, Zhonghua Yan Ke Za Zhi 2010

12 Cases, 16 Eyes

Visual Acuity: 75% Improved

ETANERCEPT

Arida et al, Semin Arthritis Rheum 2011 (review Article)

- 10 Cases Improvement
- Eyes 60%

INFLIXIMAB

Ocular Lesions: 613 Cases

1.	Sfikakis	5	Cases	2001, Lancet
2.	Sfikakis	25	“	2004, Ann Intern Med
3.	Ohno	13	“	2004, J Rheumatol
4.	Tugal-Tutkun	13	“	2005, Arthritis Rheum
5.	Wechsler	9	“	2006, 12 th ICBD
6.	Accorinti	12	“	2007, Jpn J Ophthalmol
7.	Niccoli	12	“	2007, Rheumatology (Oxford)
8.	Ozyazgan	10	“	2008, 13 th ICBD
9.	Tabbara	10	“	2008, Am J Ophthalmol
10.	Al-Rays	10	“	2008, Rheumatol Int
11.	Tanaka	19	“	2010, Nippon Ganka Gakkai Zasshi

INFLIXIMAB

Ocular Lesions: 613 Cases

12.	Yamada	17	“	2010, Brit J Ophthalmol
13.	Uhara	13	“	2010, 14 th ICBD London, UK
14.	Accorinti	10	“	2010, 14 th ICBD London, UK
15.	Giardina	21	“	2011, Rheumatol Int
16.	Taylor	107	“	2011, Am J Ophthalmol
17.	Yoshida	29	“	2012, Jpn J Ophthalmol
18.	Okada	63	“	2012, Arch Ophthalmol
19.	Keino	14	“	2013, Brit J Ophthalmol
20.	Sakai	20	“	2013, Brit J Ophthalmol
21.	Takeushi	164	“	2014, Ophthalmology
22.	Kawagushi	19	“	2014, Jpn J Ophthalmol

INFLIXIMAB

Arida et al, 2011 Semin Arthritis Rheum
(Review Article: 88 Articles, 325 patients)

Ocular Manifestations

Improved 89 %

INFLIXIMAB

Ocular Lesions: 298 Cases

- Uhara 13 Cases 2010, 14th ICBD London, UK
- Accorinti 10 “ 2010, 14th ICBD London, UK
- Yoshida 29 “ 2012, Jpn J Ophthalmol
- Okada 63 “ 2012, Arch Ophthalmol
- Takeushi 164 “ 2014, Ophthalmology
- Kawagushi 19 “ 2014, Jpn J Ophthalmol

Mean Percentage of Eyes Improved: 63%
Relapse 80% at 1 year - Side Effects: 35%

INFLIXIMAB

Taylor et al, 2011 Am J Ophthalmol

Multi Center Study

107 patients (UK-Australia), 175 Eyes, up to 10 years follow-up

- Visual Acuity Improved-Stabilized 61 %
- Mean Visual Acuity at beginning 6.1/10
- Mean Visual Acuity at 12 months 6.5/10
- Infliximab vs Azathioprine Better
 - Statistical Comparison Not Significant

Infliximab

VS

Cytotoxic Combination

COMPARISON

Infliximab vs Cytotoxic Combination

<u>Study</u>	<u>Eyes</u>	<u>VA^B</u>	<u>VA^A</u>	<u>Diff</u>	<u>Imp/Stab</u>
Taylor	175	6.1	6.5	0.4	61%
RRC	497	3.6	4.5	0.9	65%

Taylor et al, 2011 Am J Ophthalmol: Follow-up 10 years

Davatchi et al, 2014 Int J Rheum Dis: Follow-up 15 years

RRC Experience

- 5 Patients:
 - Resistant to Combination Therapy
 - 4 PCP-AZA-Pred, 1 PCP-MTX-Pred
 - Having the Monetary Requirement for Biologics
- Visual Acuity
 - 4 improved, 1 No change, 5 Aggravated
- TADAI
 - Mean aggravated from 7.42 to 7.49 → $p=0.63$

CONCLUSION

If Resistant to DMARD Combination
Not Much Benefit from Biologics

یازدهمین کنگره سالیانه انجمن روماتولوژی ایران

ADALIMUMAB

37 PubMed Articles

Many on Very Few Cases

ADALIMUMAB

Ocular Lesions: 43 Cases

- Kappen 5 Cases 2010, 14th ICBD London
- Bawazeer 11 “ 2010, Ocular Immunol Inf
- Olivieri 4 “ 2011, Clin Exp Rheumatol
- Perra 11 “ 2012, Rheumatology (Oxford)
- Interlandi 12 “ 2014, Clin Exp Rheumatol

Mean Percentage of Eyes Improved: 80%

Data Available on 53 Eyes

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بقیه بیولوژیک ها حد اکثر پیگیری ۱۴ ماه

Sota J et al 2017. Rheumatol Int

RITUXIMAB

Anti CD-20

MabThera* - Rituxan*

RITUXIMAB

- Sadreddini 1 Case 1 Eye 2008, Mod Rheumatol
- Davatchi 10 “ 20 “ 2010, Int J Rheum Dis
- Pelegriin 1 “ 1 “ 2014, J Rheumatol
- Zhao 1 “ 0 “ 2014, Clin Rheumatol

RITUXIMAB

Davatchi et al, 2010, Int J Rheum Dis
(ClinicalTrial.gov ID: NCT00664599)

- Method: RCT
 - Resistant Cases of Retinal Vasculitis (Macular Edema)
 - Single Blinded, 20 patients
 - Rituximab VS Cytotoxic Combination Therapy

RITUXIMAB

Results

Davatchi et al, 2010, Int J Rheum Dis

- Visual Acuity at 6 Months (Snellen chart on 10)

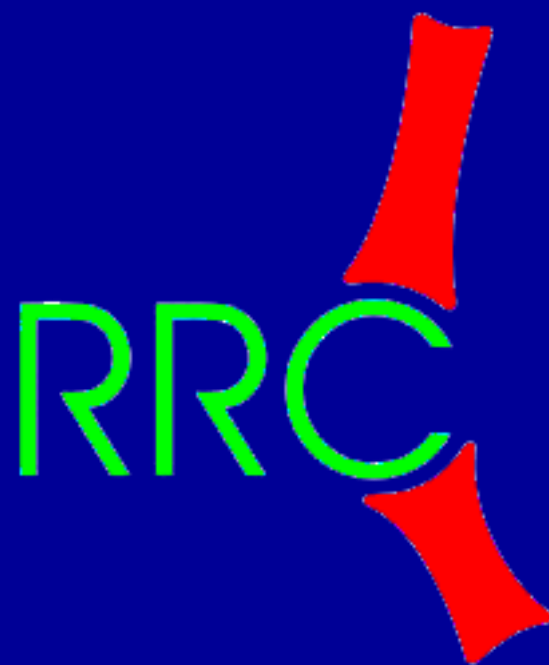
	<u>Before</u>	<u>After</u>	<u>Difference</u>	<u>Better</u>	<u>Same</u>	<u>Worse</u>
– <u>Rituximab</u> :	4.67	4.36	-0.31	20 %	10 %	70 %
– <u>Cytotoxic</u> :	4.20	4.14	-0.06	30 %	10 %	60 %

- Total Adjusted Disease Activity Index at 6 Months

	<u>Before</u>	<u>After</u>	<u>t Test</u>	<u>p Value</u>
– <u>Rituximab</u> :	44.2	35.3	4.498	0.001
– <u>Cytotoxic</u> :	42.7	39.8	1.462	0.178

نتیجه گیری کلی

- نمیتوان درمان سایتوتوکسیک را با بیولوژیک مقایسه نمود
- باید درمان طولانی چندین ساله با بیولوژیک ها هم داشت
- باید در شرایط مساوی مقایسه گردند
- در آنصورت میتوان اندیکاسیون هر یک را تعیین نمود



Behcet's Disease Unit

Rheumatology Research Center

Tehran University for Medical Sciences